# Industria y Comercio

SUPERINTENDENCIA

PLT

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD

# PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-122832

54. **TÍTULO** COMPUESTO HETEROCICLICO

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** TAKEDA PHARMACEUTICALS COMPANY LIMITED

**DOMICILIO** OSAKA, JAPON

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

22. **BOGOTÁ, D.C.,**

(FORMA P-10)

T.H.
05-10-2010

Industria y Comercio
SUPERINTENDENCIA

# PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-122832- -00000-0000
Fecha: 2010-10-04 17:26:31 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1769

## 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: **TAKEDA PHARMACEUTICAL COMPANY LIMITED**
Sociedad constituida y existente bajo las leyes de Japón.

Dirección: 1-1, Doshomachi 4-chome,
Chuo-ku, Osaka-shi,
Osaka 541-0045,
Japón

Domicilio: Osaka,
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. **Yoshihiro BANNO**
c/o Takeda Pharmaceutical Company Limited
17-85, Jusohonmachi 2-chome,
Yodogawa-ku, Osaka-shi,
Osaka 532-8686,
Japón

2. **Ryoma HARA**
c/o Takeda Pharmaceutical Company Limited
17-85, Jusohonmachi 2-chome,
Yodogawa-ku, Osaka-shi,
Osaka 532-8686,
Japón

3. **Ryosuke TOKUNOH**
c/o Takeda Pharmaceutical Company Limited
17-85, Jusohonmachi 2-chome,
Yodogawa-ku, Osaka-shi,
Osaka 532-8686,
Japón

**5 PCT (86)**

Solicitud Internacional No. PCT/JP2009/054095 Fecha: 04 de marzo de 2009
Publicación Internacional No. WO 2009/110520 A1 Fecha: 11 de septiembre de 2009

**6 Título (54)**

**COMPUESTO HETEROCÍCLICO** (F.-1772)

**7 Clasificación Internacional (51)** C07D 209/014, 495/04, 491/048
A61K 31/437 A61P 43/00 A61P 3/10

**8 Prioridad** SI ☒ NO ☐

| (33) País de Origen | (32) Fecha | (31) Número de Solicitud |
|---|---|---|
| JP | 05 de marzo de 2008 | 2008-055250 |
| JP | 06 de febrero de 2009 | 2009-025511 |

9

**Comprobante de pago No.:** 10-78,550 **Fecha:** 20 de septiembre de 2010
**Comprobante de pago No.:** 10-80,736 **Fecha:** 27 de septiembre de 2010
**Comprobante de pago No.:** 10-80,737 **Fecha:** 27 de septiembre de 2010

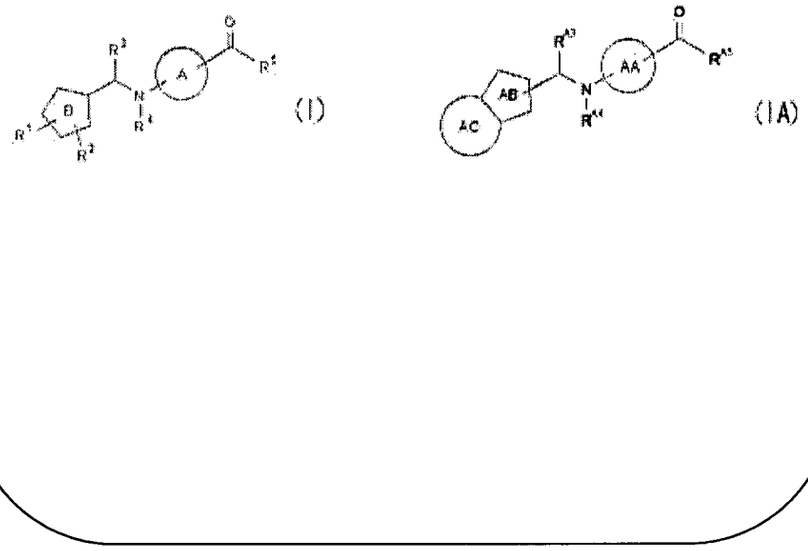
10

## Anexos:

- [x] Comprobante de pago de la tasa de presentación de la solicitud por $ 554.000.oo.
- [x] Comprobante de pago por 13 reivindicaciones adicionales después de la décima reivindicación por $338.000.oo.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [x] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar 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.
- [x] 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.
- [x] Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

## FIGURA CARACTERÍSTICA



(I) (IA)

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

## DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2009/110520 A1

   Descripción:

   Páginas 766 en el idioma original

   Páginas 955 en español

   Reivindicaciones: Número (s) 23

   Figuras: Número (s)

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

3. ☒ Listado de Secuencias.

4. ☒ Extracto de publicación.

# NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, D.C. - COLOMBIA

179

**Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.**

**Representation and Power-of- Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.**

## REPRESENTACION Y PODER

## REPRESENTATION AND POWER- OF- ATTORNEY

Fe

C

14656
08085

Yo (nosotros), abajo firmado (s)/I (we), the undersigned
TAKEDA PHARMACEUTICAL COMPANY LIMITED
domiciliado (s) en/of 1-1, Doshomachi 4-chome,
Chuo-ku, Osaka-shi, Osaka Japan

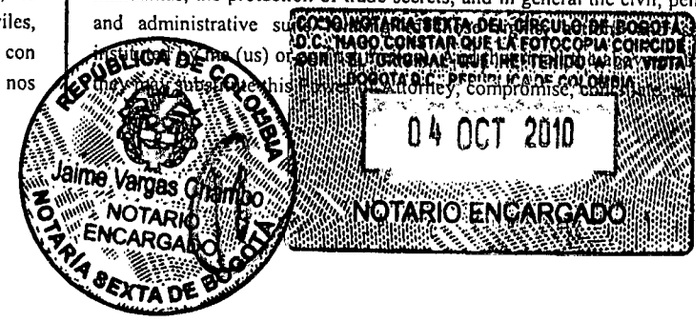
por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª Nº 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso_administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; 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 u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso_administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª Nº 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above_named attorneys_at_law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits or contentious_administrative suits related with these rights; actions and processes that we promote or that are instituted by me (us) or against me (us) or in which I (we) have to intervene; the power to act as Attorney, compromise, claim, file, submit

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promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir, este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Dado y firmado hoy/Given and signed this 14th day of December, 2004

en/in Osaka, Japan

por/by

Firma Hiroshi Akimoto Ph. D. Signature
Executive Director
Member of the Board, General Manager,
Intellectual Property Dept.
Authorized Signing Officer

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
04 OCT 2010
NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA
Jaime Vargas Chamby
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

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REGISTER NUMBER 334 / 2004

I hereby certify that this document was signed before me and that the signature appearing on the same is the true signature of Hiroshi Akimoto, Ph. D., Executive Director, Member of the Board, General Manager, Intellectual Property Department of Takeda Pharmaceutical Company Limited.

Dated this 14th day of December, 2004

10-8, Edobori 1-chome,
Nishi-ku, Osaka, Japan.

Kiyoomi Fujita

Kiyoomi Fujita
Notary attached
to The Osaka Legal
Affairs Bureau

COTEJO 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. REPÚBLICA DE COLOMBIA
04 OCT 2010
NOTARIO ENCARGADO
REPÚBLICA DE COLOMBIA
Jaime Vargas
NOTARIO
ENCARGADO
NOTARÍA SEXTA DE BOGOTÁ

# APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: **JAPAN**

   This public document

2. has been signed by — Kiyoomi FUJITA
3. acting in the capacity of — Notary Public of the Osaka Legal Affairs Bureau
4. bears the seal/stamp of — Kiyoomi FUJITA, Notary Public

Certified

5. at **Osaka**
6. DEC. 17. 2004
7. by **the Ministry of Foreign Affairs**
8. No. 04149
9. Seal/stamp:
10. Signature:

**Tsutomu HIGUCHI**

For the Minister for Foreign Affairs

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
04 OCT 2010
NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA
Jaime Vargas
NOTARIA SEXTA DE BOGOTA

大阪法務局所属　公証人役場

認証登簿　平成１６年 第　334　号

嘱託人 武田薬品工業株式会社 常務取締役　知的財産部長 秋元浩は、本職の面前でこの証書に署名した。

よって、その署名が本人の自筆であることを証する。

平成　１６　年　１２　月　１４　日

大阪市西区江戸堀１丁目１０番８号（帝人殖産ビル内）

公証人　**藤田清臣**　役場において

大阪法務局所属

公証人　藤田清臣

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
04 OCT 2010
NOTARIO ENCARGADO
REPUBLICA DE COLOMBIA
Jaime Vargas C.
NOTARIO
ENCARGADO
NOTARIA SEXTA DE BOGOTA

# THE OSAKA CHAMBER OF COMMERCE & INDUSTRY

2-8 HOMMACHIBASHI, CHUO-KU, OSAKA 540-0029, JAPAN.
FAX : (06)6944-6248 TEL : (06)6944-~~5412~~ 6411
URL : http://www.osaka.cci.or.jp/


November 17, 2004

To whom it may concern:

## CERTIFICATE OF MEMBERSHIP

This is to certify that the undermentioned company is registered as a member of this Chamber.

Company name: Takeda Pharmaceutical Company Limited

(The former company name in English was Takeda Chemical Industries, Ltd. until June 29, 2004.)

Address: 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan

Membership Number: KT-01-00080

The Osaka Chamber of Commerce & Industry

Yoshinobu Kobayashi
Authorized Signatory

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
04 OCT 2010
NOTARIO ENCARGADO

REPÚBLICA DE COLOMBIA
Jaime Vargas
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

A №009149

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2005 FEB -4 A 2:37

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

**EMBAJADA DE COLOMBIA - SECCION CONSULAR**

Tokio, Japón, DICIEMBRE 20, 2004
No. 299

El encargado de las funciones consulares de Colombia

CERTIFICA:

Que el (la) Señor(a) YOSHINOBU KOBAYASHI, quien autoriza el presente documento , es la persona legalmente facultada para representar en la fecha señalada al (a la) CAMARA DE COMERCIO E INDUSTRIA, OSAKA y que la firma y sello que en el documento aparecen como suyos son las que usa y acostumbra para sus actos oficiales.

El Encargado de Funciones Consulares no asume responsabilidad alguna por el contenido del documento.

Firma del Encargado de Funciones Consulares)

**RAFAEL RICARDO OROZCO**
**Segundo Secretario**

MINISTERIO DE RELACIONES EXTERIORES

085749

ESTA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA AS FUNCIONES INDICADAS

COBRO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. NADA CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA BOGOTA D.C. REPUBLICA DE COLOMBIA $23.oo

04 OCT 2010

NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA
Jaime Vargas
NOTARIA SEXTA DE BOGOTA

総第 3603 号

# 証　　明

大阪法務局所属公証人　藤田清臣

平成 16年12 月14 日付

平成16年 登簿 第 334 号

この認証の付与は，在職中の公証人がその権限に基づいてしたものであり，かつ，その押印は，真実のものであることを証明する。

平成16年12月17日
平成　　年　　月　　日

大阪法務局長　梅津和宏

CERTIFICATE

This is to certify that the annexed Notarial Certificate has been executed by Notary,duly authorized and practising in Osaka, Japan, and that the Official seal appearing on the same is genuine.

Date 04.12.17

Director of the Osaka Legal Affairs Bureau

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
04 OCT 2010
NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA
Jaime Vargas
NOTARIA SEXTA DE BOGOTA

TRADUCCIÓN OFICIAL No. 02.04/05b realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia y registrado ante el Ministerio de Relaciones Exteriores de Colombia.

---

A continuación se traducen los sellos y legalizaciones de un documento por medio del cual **TAKEDA PHARMACEUTICAL COMPANY LIMIMTED** domiciliado en el 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka, Japón, otorga derechos de Representación y Poder a los Doctores EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PÁEZ, tpa. 23555; y GERMÁN CAVELIER, tpa. 832, domiciliados en la Carrera 4 No. 72-35, Bogotá, Colombia.

Dado y firmado el 14 de diciembre de 2004 en Osaka, Japón.

*Firma Ilegible*

Firma Hiroshi Akimoto Ph. D.
Director Ejecutivo
Miembro de la Junta, Gerente General,
Departamento de Propiedad Intelectual
Signatario Autorizado

---

REGISTRO NÚMERO **334** / 2004

Por el presente certifico que este documento fue firmado ante mí y que la firma que aparece en el mismo es la firma auténtica de Hiroshi Akimoto, Ph. D., Director Ejecutivo, Miembro de la Junta, Gerente General, Departamento de [illegible] de Takeda Pharmaceutical Compa[illegible]

Expedido hoy 14 de [illegible] 2004

10-8, Edobori 1-chome

REPÚBLICA DE COLOMBIA
Jaime Vargas C.
NOTARIO ENCARGADO
NOTARÍA SEXTA DE BOGOTÁ

COMO NOTARÍA SEXTA DEL CÍRCULO DE BOGOTÁ D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTÁ D.C. - REPÚBLICA DE COLOMBIA
04 OCT 2010
NOTARIO ENCARGADO

Nishi-ku, Osaka, Japón

*Firma ilegible*

Kiyoomi Fujita
Notario adjunto a la
Oficina de Asuntos Legales de Osaka

DOCUMENTO ANTERIOR EN JAPONÉS

(Anexo)

Texto en Japonés

CERTIFICADO

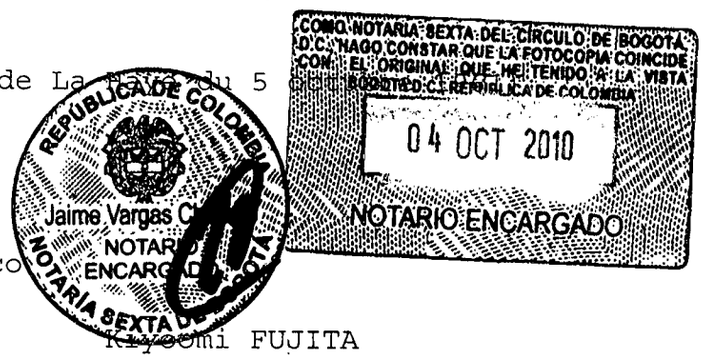
El presente es para certificar que el Certificado Notarial anexo ha sido suscrito por un notario debidamente autorizado y en ejercicio en Osaka, Japón, y que el sello oficial que aparece en el mismo es auténtico.

Fecha: 04.12.17

Director de la Oficina de Asuntos Legales de Tokio

# APOSTILLA

(Convention de La Haye du 5 [illegible]




1. País: **JAPÓN**

   Este documento público

2. ha sido firmado por Kiyoomi FUJITA

3. actuando en calidad de Director de la Oficina de Asuntos Legales de Tokio

4. lleva el sello/estampilla de Kiyoomi FUJITA, Notario Público

La Cámara de Comercio e Industria de Osaka

*Firma Ilegible*

Yoshinobu Kobayashi

Signatario Autorizado

---

(Respaldo)

Certificado No. 299 del 20 de diciembre de 2004 expedido por la EMBAJADA DE COLOMBIA en Tokio, Japón, en donde se certifica que YOSHINOBU KOBAYASHI está legalmente facultado para firmar a nombre de la Cámara de Comercio e Industria de Osaka y que su firma en el anterior documento es auténtica.

Firmado por RAFAEL RICARDO OROZCO, Segundo Secretario.

Pagados los derechos consulares.

---

Legalización de la firma anterior con el **No. 085749** expedida por el Jefe de Legalizaciones del Ministerio de Relaciones Exteriores en Santafe de Bogotá el 4 de febrero de 2005.

---

Es traducción fiel y [illegible] deja copia en esta oficina para su confr[illegible]ción.

DVZ/ID-6472/WPCL002G/

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
04 OCT 2010
NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA
Jaime Vargas [illegible]
NOTARIO
ENCARGADO
NOTARIA SEXTA DE BOGOTA

Diego F. Vargas

DIEGO F. VARGAS Z.
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES – INGLES - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S) DE

Diego Vergara

COINCIDE(N) CON LA FIRMA REGISTRADA POR EL (ELLOS) EN ESTA NOTARIA

SANTAFE DE BOGOTA, 08 FEB 2005

CODEX JURIS CIVILIS

REPUBLICA DE COLOMBIA
Notario Sexto
SANTAFE DE BOGOTA, D.C.

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2005 FEB -8 P 2:40

JEFE DE LEGALIZACIONES
BOGOTA D.C.

MINISTERIO DE RELACIONES EXTERIORES

313395

FIRMA QUE APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

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

04 OCT 2010

NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA
Jaime Vargas
NOTARIA SEXTA DE BOGOTA

**Certificado**

5. en **Osaka** 6. DIC 17 DE 2004

7. por el **Ministerio de Relaciones Exteriores**

8. **No. 04149**

DIEGO F. VARGAS
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES – INGLES - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

9. **Sello/estampilla** 10. **Firma:**

MINISTERIO DE RELACIONES EXTERIORES · JAPÓN ·

*Firma Ilegible*

*Tsutomu HIGUCHI*

**Por el Ministro de Relaciones Exteriores**

---

LA CÁMARA DE COMERCIO E INDUSTRIA DE OSAKA
2-8 HOMMACHIBASHI, CHUO-KU, OSAKA 540-0029, JAPÓN
FAX: (06) 6944-6248 TEL: 6944-~~5412~~ 6411
URL: http://www.osaka.cci.or.jp/

Noviembre 17 de 2004

A quién pueda interesar:

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
04 OCT 2010
NOTARIO ENCARGADO

CERTIFICADO DE MEMBRESÍA

El presente es para certificar que [illegible] está registrada como miembro de esta Cámara.

REPUBLICA DE COLOMBIA
Jaime Vargas
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

Nombre de la compañía: Take[illegible]ical Company Limited

(El nombre anterior de la compañía en inglés fue Takeda Chemical Industries, Ltd. hasta el 29 de junio de 2004.)

Dirección: 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japón

Número de Membresía: KT-01-00080

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA HAGO CONSTAR QUE LA(S) FIRMA(S) DE

Diego Fernando Vargas

CORRESPONDE A LA PERSONA QUE LA HA ESTAMPADO EN EL(LOS) EN ESTA NOTARIA

SANTAFE DE BOGOTA, 08 FEB 2005

CODEX JURIS CIVILIS

MINISTERIO DE RELACIONES EXTERIORES

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2005 FEB -8 P 2:39

JEFE DE LEGALIZACIONES BOGOTA D.C.

3133911

Diego Vargas APARECE EN EL DOCUMENTO DESEMPEÑA DESIGNADAS

REPUBLICA DE COLOMBIA

Jaime Vargas NOTARIO ENCARGADO

NOTARIA SEXTA DE BOGOTA

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

04 OCT 2010

NOTARIO ENCARGADO

CAVELIER
ABOGADOS

EDIFICIO SISKI
CARRERA 4 No. 72 - 35
BOGOTA 8, COLOMBIA

WEB SITE: www.cavelier.com
E-MAIL: cavelier@cavelier.com

TELEFONO: (57) (1) 347-3611
TELEFAX: (57) (1) 217-9211 (57) (1) 310-4995

Señores

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

E. S. D.

Poderdante : **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

Poder conferido el : 14/12/2004

Yo, EMILIO FERRERO, obrando como apoderado principal del poderdante arriba mencionado, mediante el presente escrito sustituyo el poder a mi otorgado a la doctora LUZ CLEMENCIA DE PAEZ, identificada con cédula de ciudadanía No. 35.456.344 y Tarjeta Profesional N°23.555, con todas las facultades que me fueron conferidas.

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil.

Señora Jefe,

EMILIO FERRERO
T.P.A. N° 31
C.C. N° 438.[illegible] de Usaquen

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
04 OCT 2010
NOTARIO ENCARGADO

Acepto:

LUZ CLEMENCIA DE PAEZ
T.P.A. N° 23.555
C.C. No. 35.456.344 de Usaquen

REPUBLICA DE COLOMBIA
Jaime Vargas
NOTARIO
ENCARGADO
NOTARIA SEXTA DE BOGOTA

**NOTARIA SEXTA DE BOGOTA**

**RECONOCIMIENTO Y PRESENTACION PERSONAL**

Bogotá, D.C. 05 NOV 2009

Ante mi AMPARO QUINTERO ARTURO,

NOTARIA SEXTA DEL CÍRCULO DE BOGOTÁ, D.C.

Compareció(eron) Emilio Torres Villarreal, Luz Clemencia Sánchez de Paez

Quien(es) exhibió(eron) la(s) C.C. 438019 T.P. 31924, 39456344 T.P. 23565

Y declaró(aron) que la(s) firma(s) que aparece(n) en el presente documento es(son) la(s) suya(s) y que el contenido del mismo es cierto.

En constancia se firma esta diligencia.

Emilio Torres
Luz Clemencia Sánchez

REPÚBLICA DE COLOMBIA
Amparo Quintero Arturo
NOTARIA
NOTARÍA SEXTA DE BOGOTÁ

DESPACHO NOTARIA SEXTA DEL CIRCULO DE BOGOTA
HACIENDO CONSTAR QUE LA FOTOCOPIA COINCIDE
CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C., REPUBLICA DE COLOMBIA
04 OCT 2010
NOTARIO ENCARGADO

REPÚBLICA DE COLOMBIA
Jaime Vargas
NOTARIO
ENCARGADO
NOTARÍA SEXTA DE BOGOTÁ

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a Nº 72-35
BOGOTA, 8 – COLOMBIA

374

F= 17

## CESION

, (nosotros) abajo firmado (s)

2.
3.

domiciliado(s) en

de la invención:

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad

constituida y existente de conformidad con las leyes de

domiciliada en

todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente de invención correspondiente en la República de Colombia.

## ASSIGNMENT

I (we), the undersigned

1. Yoshihiro BANNO
2. Ryoma HARA
3. Ryosuke TOKUNOH

of

c/o Takeda Pharmaceutical Company Limited,
17-85, Jusohonmachi 2-chome, Yodogawa-ku,
Osaka-shi, Osaka 532-8686 Japan

state(s) under oath to be sole and true inventor(s) of the invention:

HETEROCYCLIC COMPOUND

state as well, that assign, without reservations or limitations in favour of

Takeda Pharmaceutical Company Limited

a corporation constituted and existing in conformity with the laws of

Japan

domiciled in 1-1, Doshomachi 4-chome, Chuo-ku,
Osaka-shi, Osaka 541-0045 Japan

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent invention, in the Republic of Colombia

Dado y firmado hoy/Given and signed this

____ day of _____ 2010

en/in _____

Firma/Signature

1. Yoshihiro Banno Yoshihiro BANNO

2. Ryoma Hara Ryoma HARA

3. Ryosuke Tokunoh Ryosuke TOKUNOH

© CAVELIER ABOGADOS

# APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: **JAPAN**

   This public document

2. has been signed by — Masaharu KEMMA

3. acting in the capacity of — Notary Public of the Osaka Legal Affairs Bureau

4. bears the seal/stamp of — Masaharu KEMMA, Notary Public

Certified

5. at **Osaka**

6. AUG. 20. 2010

7. by **the Ministry of Foreign Affairs**

8. No. 4921

9. Seal/stamp:

10. Signature:

Naomi ASANO

For the Minister for Foreign Affairs

18

大阪法務局所属　公証人役場

認証登簿　平成２２年 第　388　号




嘱託人　阪野　義広、原　亮磨　および　得能　僚資　は、本職の面前でこの証書に署名した。

よって、その署名が本人の自筆であることを証する。

平成　２２　年　８　月　１９　日

大阪市西区江戸堀１丁目１０番８号

公証人　見　満　正　治　役場において

大阪法務局所属

公証人　見満正治

19

REGISTER NUMBER 388 / 2010

I hereby certify that this document was signed before me and that the signatures appearing on the same are the true signatures of Messrs. Yoshihiro BANNO, Ryoma HARA and Ryosuke TOKUNOH.

Dated this 19th day of August, 2010

10-8, Edobori 1-chome,

Nishi-ku, Osaka, Japan.

Masaharu Kemma

Masaharu KEMMA

Notary attached

to The Osaka Legal Affairs Bureau

Masaharu Kemma
OSAKA LEGAL AFFAIRS BUREAU
NOTARY
10-8, EDOBORI 1-CHOME
NISHI-KU, OSAKA, JAPAN

20

第　3645　号

# 証　明

この認証の付与は，在職中の公証人がその権限に基づいてしたものであり，かつ，その押印は，真実のものであることを証明する。

平成22年8月20日
平成　年　月　日

大阪法務局長　石　井　寛　明

Registration *No.*

## CERTIFICATE

This is to certify that the annexed Notarial Certificate has been executed by Notary, duly authorized and practising in Osaka, Japan, and that the Official seal appearing on the same is genuine.

Date AUG. 20. 2010

Director of the Osaka Legal Affairs Bureau

21

TRADUCCIÓN OFICIAL 271/2010 DE UN DOCUMENTO EN INGLÉS Y ESPAÑOL POR EL CUAL LOS ABAJO FIRMANTES, 1) YOSHIHIRO BANNO, 2) RYOMA HARA; Y 3. RYOSUKE TOKUNOH, DOMICILIADOS TODOS EN C/O TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85, JUSOHONMACHI 2-CHOME, YODOGAWA-KU, OSAKA-SHI, OSAKA 532-8686 JAPÓN, DECLARAN BAJO JURAMENTO SER LOS INVENTORES ÚNICOS Y VERDADEROS DEL INVENTO **COMPUESTO HETEROCÍCLICO** Y QUE LO CEDEN Y TRANSFIEREN SIN LIMITACIÓN A FAVOR DE LA SOCIEDAD TAKEDA PHARMACEUTICAL COMPANY LIMITED, UNA SOCIEDAD CONSTITUIDA Y EXISTENTE DE CONFORMIDAD CON LAS LEYES DE JAPÓN, DOMICILIADA EN 1-1, DOSHOMACHI 4-CHOME, CHUO-KU, OSAKA-SHI, OSAKA 541-0045, JAPÓN TODOS LOS DERECHOS INHERENTES A DICHA INVENCIÓN Y QUE LA CITADA COMPAÑÍA QUEDA FACULTADA PARA SOLICITAR EN SU NOMBRE LA PATENTE DE INVENCIÓN CORRESPONDIENTE EN LA REPUBLICA DE COLOMBIA.

DADO Y FIRMADO POR LOS TRES INVENTORES ARRIBA MENCIONADOS

NÚMERO DE REGISTRO 368/2010

Por la presente certifico que este documento fue firmado ante mi y que las firmas que aparecen en el mismo son las firmas verídicas de los señores YOSHIHIRO BANNO, RYOMA HARA Y RYOSUKE TOKUNOH.

Fechado hoy 19 de agosto de 2010.

10-8, Edobori 1-chome, Nishi-ku, Osaka, Japón.

FIRMADO: MASAHARU KEMMA, notario adjunto a la oficina de asuntos jurídicos de Osaka.

SELLO: MASAHARUKEMMA. OFICINA DE ASUNTOS JURÍDICOS DE OSAKA. NOTARIO, 10-8, EDOBORI 1-CHOME, NISHI-KU, OSAKA, JAPÓN

CERTIFICACIÓN

Eduardo Calado N.

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

22

Por la presente se certifica que la certificación notarial adjunta ha sido firmada por un notario debidamente autorizado y practicante en Osaka, Japón y que el sello oficial que aparece en la misma es genuino. 20 de agosto de 2010.

Director de la Oficina de Asuntos jurídicos de Osaka.

APOSTILLA

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

1. PAIS: JAPÓN

Este documento público

2. ha sido firmado por MASAHARU KEMMA

3. quien actúa en su calidad de NOTARIO PÚBLICO DE LA OFICINA DE ASUNTOS JURÍDICOS DE OSAKA

4. lleva el sello/estampilla de MASAHARU KEMMA, NOTARIO PÚBLICO

CERTIFICADO

5. En OSAKA. 6. el 20 de agosto de 2010

7. Por el Ministerio de Asuntos Exteriores

8. No. 4921

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

10. Firma: NAOMI ASANO, a nombre del Ministro de Asuntos Exteriores, COLO-14656-841-063-4. 1 hora, 500 palabras

Bogotá, 13 de septiembre de 2010.

ECN\ECN\ID-178338\WPCL002G

Eduardo Calado N.

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

(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 9 月 11 日(11.09.2009)

PCT

(10) 国際公開番号
WO 2009/110520 A1

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|---|---|
| *C07D 209/14* (2006.01) | *A61P 43/00* (2006.01) |
| *A61K 31/343* (2006.01) | *C07D 231/12* (2006.01) |
| *A61K 31/381* (2006.01) | *C07D 231/20* (2006.01) |
| *A61K 31/404* (2006.01) | *C07D 231/56* (2006.01) |
| *A61K 31/415* (2006.01) | *C07D 235/14* (2006.01) |
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| *A61K 31/4184* (2006.01) | *C07D 333/58* (2006.01) |
| *A61K 31/4355* (2006.01) | *C07D 401/04* (2006.01) |
| *A61K 31/4365* (2006.01) | *C07D 471/04* (2006.01) |
| *A61K 31/437* (2006.01) | *C07D 491/048* (2006.01) |
| *A61K 31/4439* (2006.01) | *C07D 495/04* (2006.01) |
| *A61P 3/10* (2006.01) | |

(21) 国際出願番号: PCT/JP2009/054095

(22) 国際出願日: 2009 年 3 月 4 日(04.03.2009)

(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 2008-055250 2008 年 3 月 5 日(05.03.2008) JP
特願 2009-025511 2009 年 2 月 6 日(06.02.2009) JP

(71) 出願人 (米国を除く全ての指定国について): 武田薬品工業株式会社(TAKEDA PHARMACEUTICAL COMPANY LIMITED) [JP/JP]; 〒5410045 大阪府大阪市中央区道修町四丁目１番１号 Osaka (JP).

(72) 発明者; および

(75) 発明者/出願人 (米国についてのみ): 阪野 義広(BANNO, Yoshihiro) [JP/JP]; 〒5328686 大阪府大阪市淀川区十三本町二丁目１７番８５号 武田薬品工業株式会社内 Osaka (JP). 原 亮磨(HARA, Ryoma) [JP/JP]; 〒5328686 大阪府大阪市淀川区十三本町二丁目１７番８５号 武田薬品工業株式会社内 Osaka (JP). 得能 僚資(TOKUNOH, Ryosuke) [JP/JP]; 〒5328686 大阪府大阪市淀川区十三本町二丁目１７番８５号 武田薬品工業株式会社内 Osaka (JP).

(74) 代理人: 高島 一(TAKASHIMA, Hajime); 〒5410044 大阪府大阪市中央区伏見町四丁目１番１号 明治安田生命大阪御堂筋ビル Osaka (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).

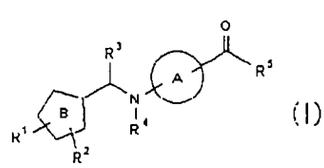
添付公開書類:

— 国際調査報告（条約第 21 条(3)）

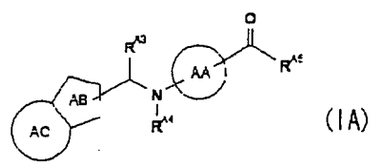
— 明細書の別個の部分として表した配列リスト（規則 5.2(a)）

(54) Title: HETEROCYCLIC COMPOUND

(54) 発明の名称: 複素環化合物



(I)



(IA)

(57) Abstract: Disclosed is an agent for prevention and treatment of diabetes, which has excellent medicinal effects. Specifically disclosed is a compound represented by formula (I) or (IA), or a salt thereof. (In the formulae, the symbols are as defined in the description.)

(57) 要約: 優れた薬効を有する糖尿病の予防または治療剤を提供すること。 式（Ｉ）または（ＩＡ）［式中の各記号は、明細書に記載の通りである。］ で表される化合物もしくはその塩。

WO 2009/110520 A1

# DESCRIPTION

## HETEROCYCLIC COMPOUND

[0001]

(Technical Field)

The present invention relates to a heterocyclic compound having a glucagon antagonistic action, which is useful for the prophylaxis or treatment of diabetes and the like.

[0002]

(Background of the Invention)

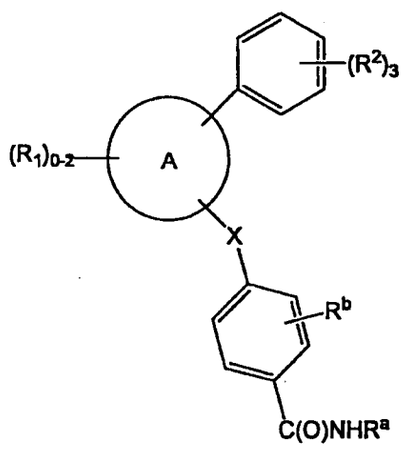
Glucagon is a straight chain peptide hormone having 29 amino acids, which is secreted from pancreatic α cells and promotes glycogenolysis and gluconeogenesis in the liver. Diabetes patients generally show promoted secretion and reactiveness of glucagon, which is one cause of hyperglycemia. Therefore, glucagon receptor antagonists can suppress excess sugar production from the liver by shutting off the action of glucagons, and are useful as therapeutic drugs for diabetes.

[0003]

As glucagon antagonists, the following compounds are known.

1) a compound represented by the following formula:

[0004]




[0005]

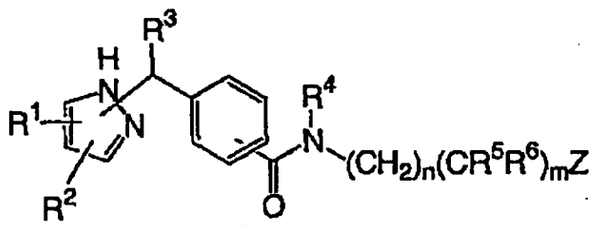
wherein ring A is 6- to 10-membered aryl, 6- to 10-membered aromatic heterocyclic group, 6-membered aryl condensed with 5-

or 6-membered carbocycle; $R_1$ is, when it is present, (a) halogen, OH, $CO_2R^4$, $SO_pR^5$, CN, $NO_2$, $C(O)NR^6R^7$ or $NR^6R^7$, (b) $C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl or $C(O)C_{1-6}$ alkyl (substitutable with (a)), (c) 6- to 10-membered aryl, aryloxy or arylthio, or 5- to 10-membered aromatic heterocyclic group, aromatic heterocyclyl-oxy or aromatic heterocyclyl-thio (each substitutable with (a) or (b); these groups are further substitutable with pyrazole, imidazole, tetrazole, pyrrole, triazole, thiazole, furan, thiophene, thiadiazole or oxazole (each substitutable with (a) or (b))); $R^2$ is H, or substituent (a) or (b); X is -O-, -S-, $-(C(R^3)_2)_{1-2}-$, $-OC(R^3)_2-$ or $-C(R^3)_2O-$; $R^3$ is H, or $C_{1-10}$ alkyl, $C_{2-4}$ alkenyl, aryl or aromatic heterocyclic group (substitutable with (a) or (b); one of $R^3$ is other than H or $C_{1-10}$ alkyl); $R^4$ is H or $C_{1-6}$ alkyl; $R^5$ is $C_{1-10}$ alkyl, aryl or aryl-$C_{1-10}$ alkyl; $R^6$ and $R^7$ are each H or $C_{1-3}$ alkyl; p is 0 - 2; $R^a$ is $CH_2CH_2CO_2R^4$, $CH_2CH(OH)CO_2R^4$ or 5-tetrazolyl; and $R^b$ is H, or substituent (a) or (b)] (patent document 1: WO2006/102067).

[0006]

2) A compound represented by the following formula:

[0007]




[0008]

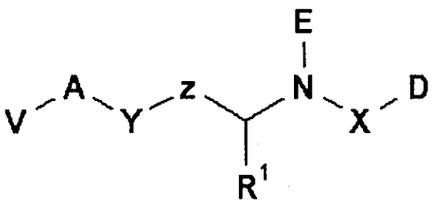
wherein $R^1$ is (a) $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl or $C_{2-10}$ alkynyl (each substitutable), or (b) aryl, aromatic heterocyclic group or nonaromatic heterocyclic group (each substitutable); $R^2$ is H or $R^1$; $R^3$ and $R^4$ are each H or $C_{1-10}$ alkyl; $R^5$ is H or F; $R^6$ is H, OH, F or $C_{1-3}$ alkyl, or $R^5$ and $R^6$ form oxo; $R^8$ is H, or $C_{1-10}$ alkyl (substitutable with phenyl, OH, $OC_{1-6}$ alkyl, $CO_2H$, $CO_2C_{1-6}$ alkyl, halo); m is 0 - 2; n is 1 - 6; when one of m and n is other than 0, Z is $COR^8$, 5-tetrazolyl or 5-(2-oxo-1,3,4-oxadiazolyl), and when m and n are both 0, Z is 5-tetrazolyl or 5-(2-oxo-

1,3,4-oxadiazolyl)] (patent document 2: WO2004/069158).

[0009]

3) A compound represented by the following formula:

[0010]

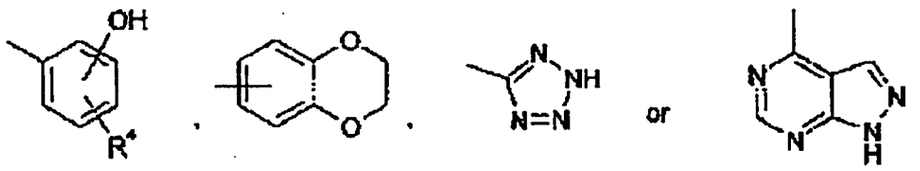


(I)

[0011]

wherein V is $-C(O)OR^2$, $-C(O)NR^2R^3$, $-C(O)NR^2OR^3$, $-S(O)_2OR^2$,

[0012]

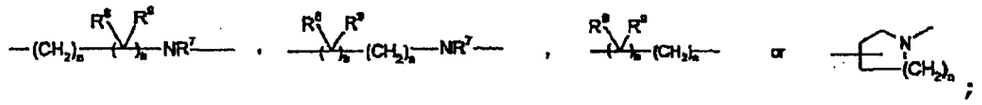


;

[0013]

$R^2$ and $R^3$ are each independently H or $C_{1-6}$ alkyl; $R^4$ is H, halogen and the like; A is

[0014]

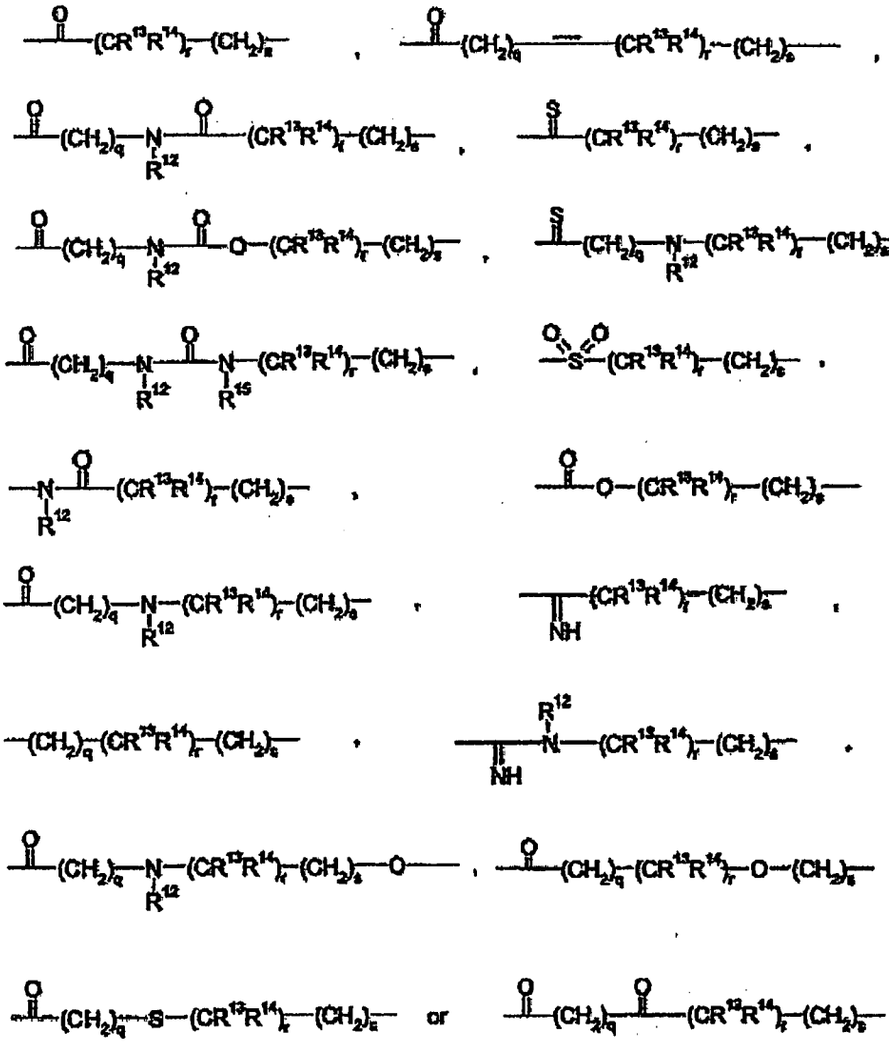


;

[0015]

b is 0 or 1; n is 0 - 3; $R^7$ is H, $C_{1-6}$ alkyl and the like; $R^8$ and $R^9$ are each independently H or $C_{1-6}$ alkyl; Y is $-C(O)-$, $-S(O)_2-$, $-O-$ or a bond; Z is phenyl, 5 - 6-membered aromatic heterocycle (each substitutable with halo etc.); $R^1$ is H or $C_{1-6}$ alkyl; X is

[0016]

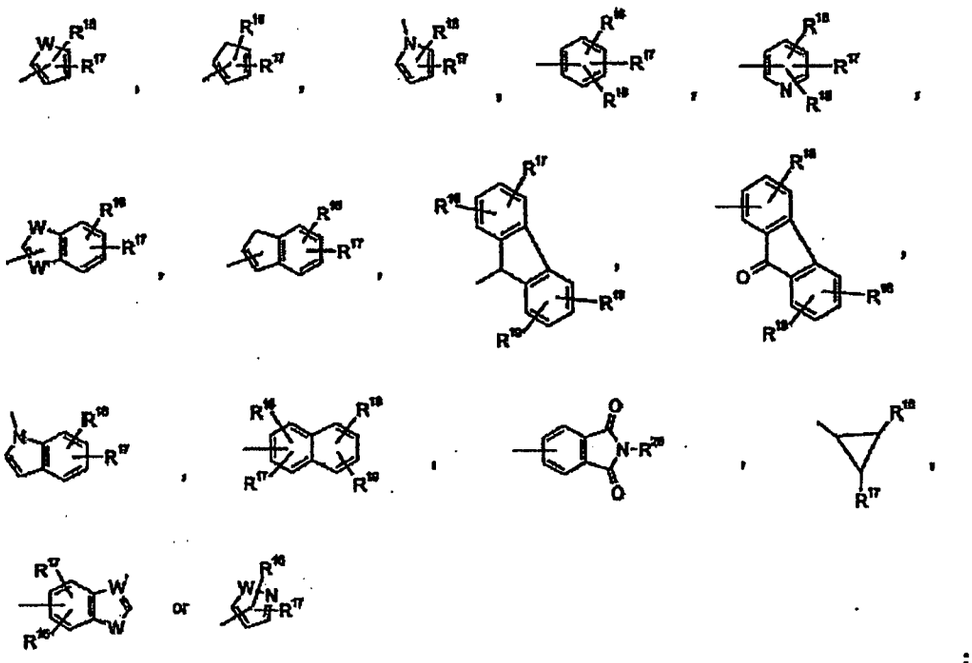


;

[0017]

r is 0 or 1; q and s are each 0 - 3; $R^{12}$, $R^{13}$, $R^{14}$ and $R^{15}$ are each independently H or $C_{1-6}$ alkyl; D is

[0018]



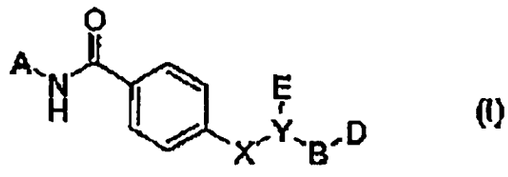
[0019]

W is -O-, -S-, $-S(O)_2-$ or $-NR^{20}-$; W' is $=CR^{20'}-$ or -N=; $R^{16}$, $R^{17}$, $R^{18}$ and $R^{19}$ are each independently H, $-C(O)NR^{21}R^{22}$, $-C(O)R^{21}$ and the like; $R^{20}$ and $R^{20'}$ are each H, $C_{1-6}$ alkyl, $C_{3-8}$ cycloalkyl or $C_{3-8}$ cycloalkyl-$C_{1-6}$ alkyl; $R^{21}$ and $R^{22}$ are each H, $-CF_3$, $C_{1-6}$ alkyl, aryl, aromatic heterocyclic group and the like; and E is an optionally substituted 3- to 9-membered monocycle or bicyclic ring (patent document 3: WO00/69810).

[0020]

4) A compound represented by the following formula:

[0021]

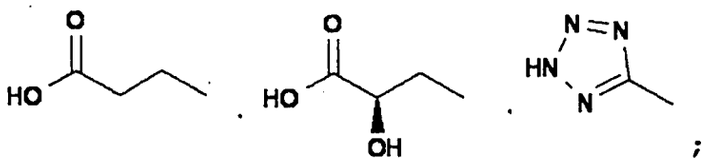


(I)

[0022]

wherein A is

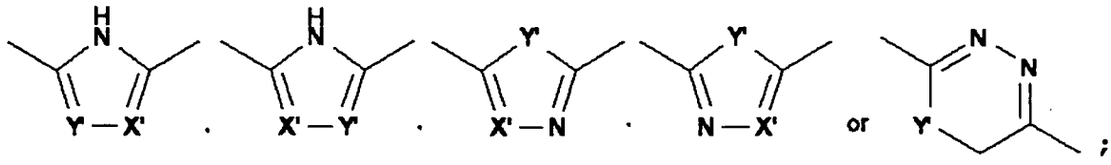
[0023]



[0024]

X is a bond, $-CR^1R^2-$ or $-NR^1-$; Y is $>CR^3-$ or $>N-$; $R^1$, $R^2$ and $R^3$ are each independently H or $C_{1-6}$ alkyl, or $R^1$ and $R^2$ optionally form a double bond; E is $C_{1-10}$ alkyl, or $C_{3-10}$ cycloalkyl, $C_{3-10}$ cycloalkyl-$C_{1-6}$ alkyl, aryl, aromatic heterocyclic group or aryl-$C_{1-6}$ alkyl (these are each substitutable with halogen, $C_{1-6}$ alkyl etc.) and the like; B is

[0025]



[0026]

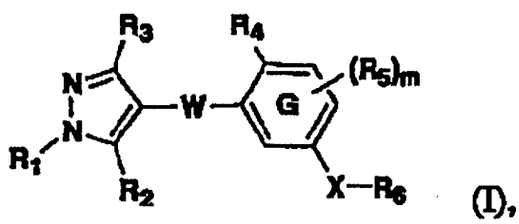
X′ is $-N=$ or $-CR^8=$; Y′ is -S-, -O- or $NR^8-$; $R^8$ is H, or $C_{1-6}$ alkyl or aryl (these are each substitutable with halogen, $C_{1-6}$ alkyl etc.); $R^9$ is H or $C_{1-6}$ alkyl; D is aryl or aromatic heterocyclic group (each substitutable with halogen, $C_{1-10}$ alkyl, $C_{1-6}$ alkoxy, $C_{3-8}$ cycloalkyl, aryl (these rings are substitutable with halogen, $C_{1-10}$ alkyl etc.) and the like) (patent document 4: WO2004/002480).

[0027]

In addition, the following compounds are known.

5) A compound represented by the following formula

[0028]

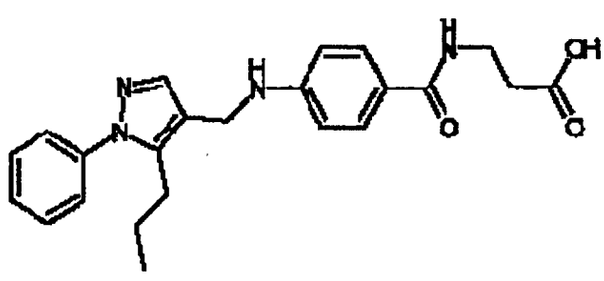


(I),

[0029]

wherein G is phenyl or pyridyl; W is $-NH(C=O)(CHR_8)_r-$, $-CH(R_8)NH-$, $-NHCH(R_8)-$, $-CH_2-O-$ or $-(C=O)O-$; $R_8$ is H or alkyl; r is 0, 1 or 2; $R_1$ is H, optionally substituted alkyl, optionally substituted aryl, optionally substituted aromatic heterocyclic group, optionally substituted cycloalkyl, optionally substituted nonaromatic heterocyclic group and the like; $R_2$ is H, optionally substituted alkyl, optionally substituted alkoxy, amino and the like; $R_3$ is H, $-CF_3$, $-OCF_3$, halogen, optionally substituted $C_{1-4}$ alkyl, $-OR_{11}$ and the like; $R_4$ is H, optionally substituted $C_{1-4}$ alkyl, halogen, $-CF_3$, $-OCF_3$, $-OR_{13}$ and the like; $R_5$ is $-CF_3$, $-OCF_3$, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted nonaromatic heterocyclic group, optionally substituted aryl, optionally substituted aromatic heterocyclic group, $-OR_{13}$, $-C(=O)R_{13}$, $-C(=O)NR_{13}R_{14}$ and the like; X is $-(C=O)NH-$, $-NH(C=O)-$, $-NH(C=O)O-$, $-SO_2NH-$, $-CO_2-$ or a bond; $R_6$ is H, optionally substituted $C_{1-4}$ alkyl, optionally substituted alkoxy, optionally substituted phenoxy, optionally substituted cycloalkyl, optionally substituted nonaromatic heterocyclic group, optionally substituted aryl, optionally substituted aromatic heterocyclic group and the like; $R_6$ and $R_5$ may be bonded to each other to form 5- or 6-membered ring; $R_{11}$, $R_{13}$ and $R_{14}$ are each independently H, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted nonaromatic heterocyclic group, optionally substituted aryl or optionally substituted aromatic heterocycle; m is 0, 1, 2 or 3, which is useful as a therapeutic agent for inflammatory diseases, specifically the following compound

[0030]



[0031]

(patent document 5: WO2004/098528).

[0032]

patent document 1: WO2006/102067

patent document 2: WO2004/069158

patent document 3: WO00/69810

patent document 4: WO2004/002480

patent document 5: WO2004/098528

Disclosure of the Invention

Problems to be Solved by the Invention

[0033]

The development of a compound having superior efficacy and useful for the prophylaxis or treatment of diabetes and the like has been desired.

Means of Solving the Problems

[0034]

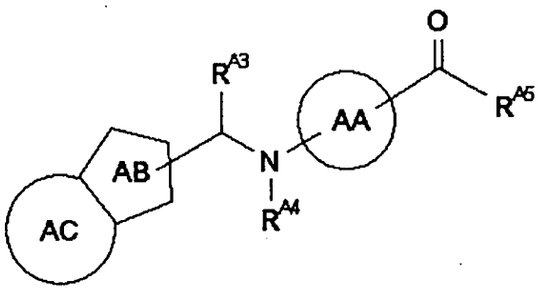
The present inventors have found that a compound represented by the following formula (I) or a salt thereof (sometimes to be abbreviated as "compound (I)" in the present specification) and a compound represented by the formula (IA) or a salt thereof (sometimes to be abbreviated as "compound (IA)" in the present specification) have superior glucagon antagonistic action, and superior efficacy as an agent for the prophylactic or treatment of diabetes and the like. Based on the finding, the present inventors have conducted intensive studies and completed the present invention.

[0035]

Accordingly, the present invention relates to

(1) a compound represented by the following formula:

[0036]




(IA)

[0037]

wherein ring AA is an optionally substituted benzene ring, or an optionally substituted 5- or 6-membered aromatic heterocycle;

ring AB is an optionally substituted 5-membered aromatic heterocycle;

ring AC is an optionally substituted benzene ring, or an optionally substituted 5- or 6-membered aromatic heterocycle;

$R^{A3}$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{3-10}$ cycloalkyl group, an optionally substituted $C_{6-14}$ aryl group or an optionally substituted heterocyclic group;

$R^{A4}$ is a hydrogen atom or a $C_{1-6}$ alkyl group;

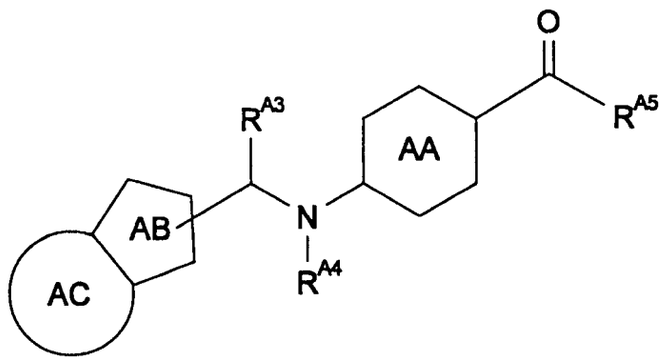
$R^{A5}$ is $-(CH_2)_3-COOR^{A11}$ or $-NR^{A6}-CR^{A7}R^{A8}-CR^{A9}R^{A10}-COOR^{A11}$;

$R^{A6}$, $R^{A7}$, $R^{A8}$, $R^{A9}$ and $R^{A11}$ are each independently a hydrogen atom or a $C_{1-6}$ alkyl group; and

$R^{A10}$ is a hydrogen atom, a $C_{1-6}$ alkyl group or a hydroxy group, or a salt thereof;

(2) the compound of the above-mentioned (1), wherein the formula (IA) is the following formula

[0038]




(IA')

, and

[0039]

ring AA is a benzene ring or 6-membered aromatic heterocycle;

(3) the compound of the above-mentioned (2), wherein $R^{A3}$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{3-10}$ cycloalkyl group, or an optionally substituted 5- or 6-membered heterocyclic group;

$R^{A4}$ is a hydrogen atom;

$R^{A5}$ is $-(CH_2)_3-COOR^{A11}$ or $-NR^{A6}-(CH_2)_2-COOR^{A11}$;

$R^{A6}$ is a hydrogen atom or methyl; and

$R^{A11}$ is a hydrogen atom, methyl or ethyl;

(4) 3-{[(4-{[cyclohexyl(3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid or a salt thereof;

(5) 3-{[(6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-yl)carbonyl](methyl)amino}propanoic acid or a salt thereof;

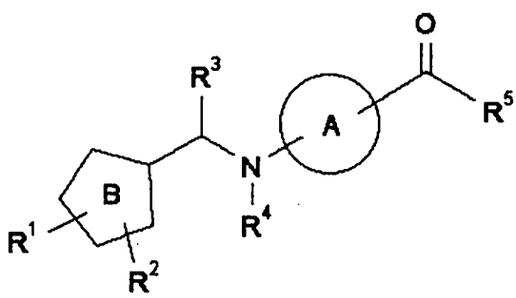
(6) 3-{[(4-{[2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid or a salt thereof;

(7) 3-[{[4-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid or a salt thereof;

(8) 3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid or a salt thereof;

(9) a compound represented by the following formula:

[0040]




(I)

[0041]

wherein ring A is an optionally substituted benzene ring, or an optionally substituted 5- or 6-membered aromatic heterocycle;

ring B is pyrazole;

$R^1$ and $R^2$ are each independently an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted hydroxy group or acyl;

$R^3$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{3-10}$ cycloalkyl group, an optionally substituted $C_{6-14}$ aryl group or an optionally substituted heterocyclic group;

$R^4$ is a hydrogen atom or a $C_{1-6}$ alkyl group;

$R^5$ is $-(CH_2)_3-COOR^{11}$ or $-NR^6-CR^7R^8-CR^9R^{10}-COOR^{11}$;

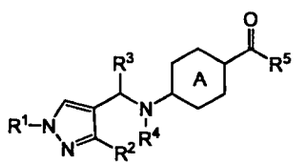
$R^6$, $R^7$, $R^8$, $R^9$ and $R^{11}$ are each independently a hydrogen atom or a $C_{1-6}$ alkyl group; and

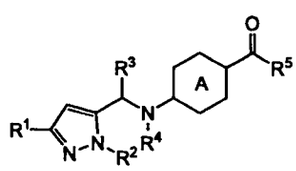
$R^{10}$ is a hydrogen atom, a $C_{1-6}$ alkyl group or a hydroxy group,

excluding N-[4-[[(1-phenyl-5-propyl-1H-pyrazol-4-yl)methyl]amino]benzoyl]-β-alanine, or a salt thereof;

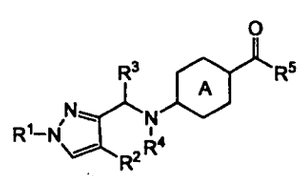
(10) the compound of the above-mentioned (9), wherein the formula (I) is the following formula

[0042]


(I')


(I'')

or


(I''')

,

[0043]

and ring A is a benzene ring or 6-membered aromatic heterocycle;

(11) the compound of the above-mentioned (9), wherein $R^1$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{6-14}$ aryl group, or an optionally substituted 5- or 6-membered aromatic heterocyclic group;

$R^2$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{1-6}$ alkoxy group, or an optionally substituted $C_{3-10}$ cycloalkyl group;

$R^3$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally

substituted $C_{3-10}$ cycloalkyl group, or an optionally substituted 5- or 6-membered heterocyclic group;

$R^4$ is a hydrogen atom;

$R^5$ is $-(CH_2)_3-COOR^{11}$ or $-NR^6-CH_2-CR^9R^{10}-COOR^{11}$;

$R^6$ is a hydrogen atom or methyl;

$R^9$ is a hydrogen atom, methyl or ethyl;

$R^{10}$ is a hydrogen atom, methyl or ethyl; and

$R^{11}$ is a hydrogen atom, methyl or ethyl;

(12) 3-[({4-[(cyclohexyl{3-methyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid or a salt thereof;

(13) 3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid or a salt thereof;

(14) 3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid or a salt thereof;

(15) a prodrug of the compound of the above-mentioned (1) or (9);

(16) a medicament comprising the compound of the above-mentioned (1) or (9) or a prodrug thereof;

(17) the medicament of the above-mentioned (16) which is a glucagon antagonist;

(18) the medicament of the above-mentioned (16) which is a sugar production-suppressive agent;

(19) the medicament of the above-mentioned (16) which is an agent for the prophylactic or treatment of diabetes;

(20) a method of suppressing sugar production in a mammal, comprising administering the compound of the above-mentioned (1) or a prodrug thereof or the compound of the above-mentioned (9) or a prodrug thereof to the mammal;

(21) a method for the prophylaxis or treatment of diabetes in

36

a mammal, comprising administering the compound of the above-mentioned (1) or a prodrug thereof or the compound of the above-mentioned (9) or a prodrug thereof to the mammal;

(22) use of the compound of the above-mentioned (1) or a prodrug thereof or the compound of the above-mentioned (9) or a prodrug thereof for the production of a medicament for suppressing sugar production;

(23) use of the compound of the above-mentioned (1) or a prodrug thereof or the compound of the above-mentioned (9) or a prodrug thereof for the production of an agent for the prophylaxis or treatment of diabetes;

and the like.

[0044]

(Effect of the Invention)

Since the compound of the present invention has a glucagon antagonistic action and superior efficacy (suppression of blood glucose increase, hypoglycemic action and the like), it is useful for the prophylaxis or treatment of diabetes and the like.

[0045]

(Detailed Description of the Invention)

In the present specification, the "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

In the present specification, examples of the "$C_{1-10}$ alkyl group" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, heptyl, octyl, nonyl, decyl and the like.

In the present specification, examples of the "$C_{1-6}$ alkyl group" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl and the like.

In the present specification, examples of the "branched $C_{1-6}$ alkyl group" include isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, neopentyl, 1-ethylpropyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl and the like.

[0046]

In the present specification, examples of the "$C_{2-10}$ alkenyl group" include ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, 5-hexenyl, 1-heptenyl, 1-octenyl and the like.

In the present specification, examples of the "$C_{2-6}$ alkenyl group" include ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, 5-hexenyl and the like.

[0047]

In the present specification, examples of the "$C_{2-10}$ alkynyl group" include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl and the like.

In the present specification, examples of the "$C_{2-6}$ alkynyl group" include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and the like.

[0048]

In the present specification, examples of the "$C_{1-6}$ alkoxy group" include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

In the present specification, examples of the "$C_{2-6}$ alkenyloxy group" include ethenyloxy and the like.

[0049]

In the present specification, examples of the "$C_{3-10}$ cycloalkyl group" include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[4.3.1]decyl, adamantyl and the like.

In the present specification, examples of the "$C_{3-6}$ cycloalkyl group" include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The $C_{3-6}$ cycloalkyl group and $C_{3-10}$ cycloalkyl group may form a fused ring group with a benzene ring and examples of such fused ring group include indanyl and the like.

In the present specification, examples of the "$C_{3-10}$ cycloalkenyl group" include cyclopropenyl (e.g., 2-cyclopropen-1-yl), cyclobutenyl (e.g., 2-cyclobuten-1-yl), cyclopentenyl (e.g., 2-cyclopenten-1-yl, 3-cyclopenten-1-yl), cyclohexenyl (e.g., 2-cyclohexen-1-yl, 3-cyclohexen-1-yl), cycloheptenyl (e.g., 2-cyclohepten-1-yl), cyclooctenyl (e.g., 2-cycloocten-1-yl) and the like.

In the present specification, examples of the "$C_{3-6}$ cycloalkenyl group" include cyclopropenyl (e.g., 2-cyclopropen-1-yl), cyclobutenyl (e.g., 2-cyclobuten-1-yl), cyclopentenyl (e.g., 2-cyclopenten-1-yl, 3-cyclopenten-1-yl), cyclohexenyl (e.g., 2-cyclohexen-1-yl, 3-cyclohexen-1-yl) and the like.

The $C_{3-6}$ cycloalkenyl group and $C_{3-10}$ cycloalkenyl group may form a fused ring group with a benzene ring and examples of such fused ring group include dihydronaphthyl and the like.

In the present specification, examples of the "$C_{4-10}$ cycloalkadienyl group" include 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl and the like.

The $C_{4-10}$ cycloalkadienyl group may form a fused ring group with a benzene ring and examples of such fused ring group include fluorenyl and the like.

In the present specification, examples of the "$C_{6-14}$ aryl group" include phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl, biphenylyl and the like.

In the present specification, examples of the "$C_{6-10}$ aryl group" include phenyl, naphthyl and the like.

In the present specification, examples of the "$C_{6-14}$ aryloxy group" include phenyloxy and naphthyloxy.

In the present specification, examples of the "$C_{7-13}$ aralkyl group" include benzyl, phenethyl, naphthylmethyl, biphenylylmethyl and the like.

In the present specification, examples of the "$C_{7-13}$ aralkyloxy group" include benzyloxy and the like.

In the present specification, examples of the "$C_{8-13}$ arylalkenyl group" include styryl and the like.

[0050]

In the present specification, examples of the "heterocyclic group" include the following aromatic heterocyclic groups and nonaromatic heterocyclic groups.

In the present specification, examples of the "aromatic heterocyclic group" include a 4- to 12- membered aromatic heterocyclic group, for example, a 4- to 7-membered (preferably 5- or 6-menbered) monocyclic aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom, and a 8- to 12- membered fused aromatic heterocyclic group. Examples of the fused aromatic heterocyclic group include a group derived from a fused ring wherein 1 or 2 rings selected from a 5- or 6-membered aromatic heterocycle containing 1 or 2 nitrogen atoms (e.g., pyrrole, imidazole, pyrazole, pyrazine, pyridine, pyrimidine), a 5-membered aromatic heterocycle containing one sulfur atom (e.g., thiophene) and a benzene ring, and a ring corresponding to a 4- to 7- membered monocyclic aromatic heterocyclic group are condensed, and the like.

[0051]

Preferable examples of the aromatic heterocyclic group include

monocyclic aromatic heterocyclic groups such as furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl), triazinyl (e.g., 1,2,4-triazin-1-yl, 1,2,4-triazin-3-yl) and the like;

fused aromatic heterocyclic groups such as quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 6-quinolyl), isoquinolyl (e.g., 3-isoquinolyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl, 6-quinoxalyl), benzofuranyl (e.g., 2-benzofuranyl, 3-benzofuranyl), benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzisoxazolyl (e.g., 7-benzisoxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-5-yl), benzotriazolyl (e.g., 1H-1,2,3-benzotriazol-5-yl), indolyl (e.g., indol-1-yl, indol-2-yl, indol-3-yl, indol-5-yl), indazolyl (e.g., 1H-indazol-3-yl), pyrrolopyrazinyl (e.g., 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyrazin-6-yl), imidazopyridinyl (e.g., 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-

2-yl, 2H-imidazo[1,2-a]pyridin-3-yl), thienopyridinyl (e.g., thieno[2,3-b]pyridin-3-yl), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl), pyrazolopyridinyl (e.g., 1H-pyrazolo[4,3-c]pyridin-3-yl), pyrazolothienyl (e.g., 2H-pyrazolo[3,4-b]thiophen-2-yl), pyrazolotriazinyl (e.g., pyrazolo[5,1-c][1,2,4]triazin-3-yl) and the like;
and the like.

[0052]

In the present specification, examples of the "non-aromatic heterocyclic group" include a 4- to 12- membered non-aromatic heterocyclic group, for example, a 4- to 7-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (the sulfur atom is optionally oxidized) and a nitrogen atom, and a 8- to 12- membered fused non-aromatic heterocyclic group. Examples of the fused non-aromatic heterocyclic group include a group derived from a fused ring wherein 1 or 2 rings selected from a 5- or 6-membered aromatic heterocycle containing 1 or 2 nitrogen atoms (e.g., pyrrole, imidazole, pyrazole, pyrazine, pyridine, pyrimidine), a 5-membered aromatic heterocycle containing one sulfur atom (e.g., thiophene) and a benzene ring, and a ring corresponding to the 4- to 7-membered monocyclic non-aromatic heterocyclic group are condensed (optionally partially saturated further), and the like.

[0053]

Preferable examples of the non-aromatic heterocyclic group include
monocyclic non-aromatic heterocyclic groups such as oxetanyl (e.g., 3- oxetanyl), pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl), piperidinyl (e.g., piperidino, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), morpholinyl (e.g., morpholino), thiomorpholinyl (e.g., thiomorpholino), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl, 3-piperazinyl), hexamethyleniminyl (e.g., hexamethylenimin-1-yl), oxazolidinyl (e.g., oxazolidin-2-

yl), thiazolidinyl (e.g., thiazolidin-2-yl), dihydrothiopyranyl (e.g., dihydrothiopyran-3-yl, dihydrothiopyran-4-yl), imidazolidinyl (e.g., imidazolidin-2-yl, imidazolidin-3-yl), oxazolinyl (e.g., oxazolin-2-yl), thiazolinyl (e.g., thiazolin-2-yl), imidazolinyl (e.g., imidazolin-2-yl, imidazolin-3-yl), dioxolyl (e.g., 1,3-dioxol-4-yl), dioxolanyl (e.g., 1,3-dioxolan-4-yl), dihydrooxadiazolyl (e.g., 4,5-dihydro-1,2,4-oxadiazol-3-yl), pyranyl (e.g., 4-pyranyl), tetrahydropyranyl (e.g., 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl), thiopyranyl (e.g., 4-thiopyranyl), tetrahydrothiopyranyl (e.g., 2-tetrahydrothiopyranyl, 3-tetrahydrothiopyranyl, 4-tetrahydrothiopyranyl), 1-oxidotetrahydrothiopyranyl (e.g., 1-oxidotetrahydrothiopyran-4-yl), 1,1-dioxidotetrahydrothiopyranyl (e.g., 1,1-dioxidotetrahydrothiopyran-4-yl), tetrahydrofuryl (e.g., tetrahydrofuran-3-yl, tetrahydrofuran-2-yl), pyrazolidinyl (e.g., pyrazolidin-1-yl, pyrazolidin-3-yl), pyrazolinyl (e.g., pyrazolin-1-yl), tetrahydropyrimidinyl (e.g., tetrahydropyrimidin-1-yl), dihydrotriazolyl (e.g., 2,3-dihydro-1H-1,2,3-triazol-1-yl), tetrahydrotriazolyl (e.g., 2,3,4,5-tetrahydro-1H-1,2,3-triazol-1-yl) and the like;

fused non-aromatic heterocyclic groups such as dihydroindolyl (e.g., 2,3-dihydro-1H-indol-1-yl), dihydroisoindolyl (e.g., 1,3-dihydro-2H-isoindol-2-yl), dihydrobenzofuranyl (e.g., 2,3-dihydro-1-benzofuran-5-yl), dihydrobenzodioxinyl (e.g., 2,3-dihydro-1,4-benzodioxinyl), dihydrobenzodioxepinyl (e.g., 3,4-dihydro-2H-1,5-benzodioxepinyl), tetrahydrobenzofuranyl (e.g., 4,5,6,7-tetrahydro-1-benzofuran-3-yl), chromenyl (e.g., 4H-chromen-2-yl, 2H-chromen-3-yl), dihydrochromenyl (e.g., 3,4-dihydro-2H-chromen-2-yl), dihydroquinolinyl (e.g., 1,2-dihydroquinolin-4-yl), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydroquinolin-4-yl), dihydroisoquinolinyl (e.g., 1,2-dihydroisoquinolin-4-yl), tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydroisoquinolin-4-yl), dihydrophthalazinyl (e.g., 1,4-dihydrophthalazin-4-yl) and the like;

and the like.

[0054]

In the present specification, examples of the "5- or 6-membered heterocyclic group" include 5- or 6-membered rings from among the above-mentioned monocyclic aromatic heterocyclic groups and monocyclic nonaromatic heterocyclic groups.

[0055]

In the present specification, specific examples of the "5- or 6-membered aromatic heterocycle" include rings corresponding to the 5- or 6-membered ring group from among the above-mentioned aromatic heterocyclic group, for example, furan, thiophene, pyridine, pyrimidine, pyridazine, pyrazine, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, oxadiazole, thiadiazole, triazole, tetrazole, triazine and the like.

In the present specification, specific examples of the "5-membered aromatic heterocycle" include rings corresponding to the 5-membered ring group from among the above-mentioned aromatic heterocyclic groups, for example, furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, oxadiazole, thiadiazole, triazole, tetrazole and the like.

[0056]

In the present specification, examples of the "4- to 12-membered aromatic heterocyclyl-oxy group" include groups wherein an oxy group is bonded to the above-mentioned 4- to 12-membered aromatic heterocyclic group, for example, pyridyloxy and the like.

In the present specification, examples of the "4- to 12-membered non-aromatic heterocyclyl-oxy group" include groups wherein an oxy group is bonded to the above-mentioned 4- to 12-membered nonaromatic heterocyclic group, for example, tetrahydropyranyloxy, tetrahydrothiopyranyloxy, 1,1-dioxidotetrahydrothiopyranyloxy and the like.

In the present specification, examples of the "4- to 12-membered aromatic heterocyclyl-carbonyl group" include groups wherein a carbonyl group is bonded to the above-mentioned 4- to 12-membered aromatic heterocyclic group, for example, furylcarbonyl, thienylcarbonyl, pyrazolylcarbonyl, pyrazinylcarbonyl, isooxazolylcarbonyl, pyridylcarbonyl, thiazolylcarbonyl and the like.

In the present specification, examples of the "4- to 12-membered non-aromatic heterocyclyl-carbonyl group" include groups wherein a carbonyl group is bonded to the above-mentioned 4- to 12-membered nonaromatic heterocyclic group, for example, tetrahydrofurylcarbonyl, pyrrolidinylcarbonyl, morpholinylcarbonyl and the like.

[0057]

In the present specification, examples of the "$C_{1-6}$ alkyl-carbonyl group" include acetyl, propanoyl, butanoyl, isobutanoyl, tert-butanoyl, pentanoyl, isopentanoyl, hexanoyl and the like.

In the present specification, examples of the "$C_{1-6}$ alkyl-carbonyloxy group" include acetyloxy, propanoyloxy, butanoyloxy, isobutanoyloxy, tert-butanoyloxy, pentanoyloxy, isopentanoyloxy, hexanoyloxy and the like.

In the present specification, examples of the "$C_{1-6}$ alkoxy-carbonyl group" include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl and the like.

In the present specification, examples of the "$C_{3-10}$ cycloalkyl-carbonyl group" include cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl and the like.

In the present specification, examples of the "$C_{6-14}$ aryl-carbonyl group" include benzoyl and the like.

In the present specification, examples of the "$C_{1-6}$ alkylthio group" include methylthio, ethylthio, isopropylthio and the like.

In the present specification, examples of the "$C_{6-14}$ arylthio group" include phenylthio, naphthylthio and the like.

In the present specification, examples of the "$C_{7-13}$ aralkylthio group" include benzylthio and the like.

In the present specification, examples of the "$C_{1-6}$ alkylsulfonyl group" include methylsulfonyl, ethylsulfonyl, isopropylsulfonyl and the like.

In the present specification, examples of the "$C_{6-14}$ arylsulfonyl group" include benzenesulfonyl and the like.

In the present specification, examples of the "$C_{1-3}$ alkylenedioxy group" include methylenedioxy, ethylenedioxy and the like.

[0058]

In the present specification, examples of the "optionally substituted hydrocarbon group" include optionally substituted $C_{1-10}$ alkyl group, optionally substituted $C_{2-10}$ alkenyl group, optionally substituted $C_{2-10}$ alkynyl group, optionally substituted $C_{3-10}$ cycloalkyl group, optionally substituted $C_{3-10}$ cycloalkenyl group, optionally substituted $C_{4-10}$ cycloalkadienyl group, and optionally substituted $C_{6-14}$ aryl group, optionally substituted $C_{7-13}$ aralkyl group, optionally substituted $C_{8-13}$ arylalkenyl group and the like.

[0059]

In the present specification, examples of the "optionally substituted hydroxy group" include a hydroxy group optionally substituted by substituent(s) selected from

(1) optionally substituted $C_{1-10}$ alkyl group (preferably, optionally substituted $C_{1-6}$ alkyl group),

(2) optionally substituted $C_{2-10}$ alkenyl group,

(3) optionally substituted $C_{3-10}$ cycloalkyl group,

(4) optionally substituted $C_{3-10}$ cycloalkenyl group,

(5) optionally substituted $C_{6-14}$ aryl group,

(6) optionally substituted $C_{7-13}$ aralkyl group,

(7) optionally substituted $C_{8-13}$ arylalkenyl group,

(8) optionally substituted $C_{1-6}$ alkyl-carbonyl group,

(9) optionally substituted heterocyclic group

and the like.

[0060]

In the present specification, the $C_{1-6}$ alkyl group, $C_{1-10}$ alkyl group, $C_{2-10}$ alkenyl group, $C_{2-10}$ alkynyl group and $C_{1-6}$ alkyl-carbonyl group of the "optionally substituted $C_{1-6}$ alkyl group", "optionally substituted $C_{1-10}$ alkyl group", "optionally substituted $C_{2-10}$ alkenyl group", "optionally substituted $C_{2-10}$ alkynyl group", and "optionally substituted $C_{1-6}$ alkyl-carbonyl group" optionally have 1 to 5 (preferably 1 to 3) substituents at each substitutable position(s).

Examples of such substituent include the following substituent group A:

(substituent group A)

(1) $C_{3-10}$ cycloalkyl group;

(2) $C_{6-14}$ aryl group optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms,

(b) hydroxy group,

(c) $C_{1-6}$ alkoxy group optionally substituted by 1 to 3 halogen atoms, and

(d) halogen atom;

(3) 4- to 12-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms,

(b) hydroxy group,

(c) $C_{1-6}$ alkoxy group optionally substituted by 1 to 3 halogen atoms, and

(d) halogen atom;

(4) 4- to 12-membered nonaromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms,

(b) hydroxy group,

(c) $C_{1-6}$ alkoxy group optionally substituted by 1 to 3 halogen

atoms,

(d) halogen atom, and

(e) oxo group;

(5) amino group optionally mono- or di-substituted by substituent(s) selected from

(a) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 substituents selected from

(i) halogen atom, and

(ii) $C_{1-6}$ alkoxy group,

(b) $C_{1-6}$ alkyl-carbonyl group optionally substituted by 1 to 3 halogen atoms,

(c) $C_{1-6}$ alkoxy-carbonyl group optionally substituted by 1 to 3 halogen atoms,

(d) $C_{1-6}$ alkylsulfonyl group optionally substituted by 1 to 3 halogen atoms,

(e) carbamoyl group optionally mono- or di-substituted by $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms, and

(f) 4- to 12-membered aromatic heterocyclic group;

(6) $C_{1-6}$ alkyl-carbonyl group optionally substituted by 1 to 3 halogen atoms;

(7) $C_{1-6}$ alkoxy-carbonyl group optionally substituted by 1 to 3 substituents selected from

(a) halogen atom,

(b) $C_{1-6}$ alkoxy group, and

(c) $C_{6-14}$ aryl group;

(8) $C_{1-6}$ alkylsulfonyl group optionally substituted by 1 to 3 halogen atoms;

(9) carbamoyl group optionally mono- or di-substituted by $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms;

(10) thiocarbamoyl group optionally mono- or di-substituted by $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms;

(11) sulfamoyl group optionally mono- or di-substituted by $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms;

(12) carboxy group;

(13) hydroxy group;

(14) $C_{1-6}$ alkoxy group optionally substituted by 1 to 3 substituents selected from

(a) halogen atom,

(b) carboxy group,

(c) $C_{1-6}$ alkoxy group,

(d) $C_{3-6}$ cycloalkyl group,

(e) $C_{1-6}$ alkoxy-carbonyl group optionally substituted by 1 to 3 $C_{6-14}$ aryl groups,

(f) amino group optionally mono- or di-substituted by substituent(s) selected from $C_{1-6}$ alkyl group and $C_{1-6}$ alkoxy-carbonyl group,

(g) 4- to 12-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from

(i) halogen atom, and

(ii) $C_{1-6}$ alkyl group,

(h) 4- to 12-membered nonaromatic heterocyclic group optionally substituted by 1 to 3 $C_{1-6}$ alkyl groups,

(i) $C_{1-6}$ alkylsulfonyl group,

(j) $C_{1-6}$ alkylthio group, and

(k) hydroxy group;

(15) $C_{2-6}$ alkenyloxy group optionally substituted by 1 to 3 halogen atoms;

(16) $C_{7-13}$ aralkyloxy group;

(17) $C_{6-14}$ aryloxy group;

(18) $C_{1-6}$ alkyl-carbonyloxy group;

(19) 4- to 12-membered aromatic heterocyclyl-oxy group optionally substituted by 1 to 3 substituents selected from

(i) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms, and

(ii) cyano group;

(20) 4- to 12-membered non-aromatic heterocyclyl-oxy group;

(21) $C_{6-14}$ aryl-carbonyl group optionally substituted by 1 to 3 substituents selected from

(a) halogen atom, and

(b) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms;

(22) 4- to 12-membered aromatic heterocyclyl-carbonyl group optionally substituted by 1 to 3 substituents selected from $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms;

(23) 4- to 12-membered non-aromatic heterocyclyl-carbonyl group optionally substituted by 1 to 3 substituents selected from $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms;

(24) mercapto group;

(25) $C_{1-6}$ alkylthio group optionally substituted by 1to 3 substituents selected from

(a) halogen atom, and

(b) $C_{1-6}$ alkoxycarbonyl group;

(26) $C_{7-13}$ aralkylthio group;

(27) $C_{6-14}$ arylthio group;

(28) cyano group;

(29) nitro group;

(30) halogen atom;

(31) $C_{1-3}$ alkylenedioxy group.

When two or more substituents are used, the respective substituents may be the same or different.

[0061]

In the present specification, the benzene ring, $C_{6-14}$ aryl group, $C_{3-10}$ cycloalkenyl group, $C_{4-10}$ cycloalkadienyl group, $C_{7-13}$ aralkyl group, and $C_{8-13}$ arylalkenyl group of the "optionally substituted benzene ring", "optionally substituted $C_{6-14}$ aryl group", "optionally substituted $C_{3-10}$ cycloalkenyl group", "optionally substituted $C_{4-10}$ cycloalkadienyl group", "optionally substituted $C_{7-13}$ aralkyl group" and "optionally substituted $C_{8-13}$ arylalkenyl group" each optionally have 1 to 5 (preferably 1 to 3) substituents at substitutable position(s).

Examples of such substituent include the following substituent group B:

(substituent group B)

(1) $C_{3-10}$ cycloalkyl group;

(2) $C_{6-14}$ aryl group optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms,

(b) hydroxy group,

(c) $C_{1-6}$ alkoxy group optionally substituted by 1 to 3 halogen atoms, and

(d) halogen atom;

(3) 4- to 12-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms,

(b) hydroxy group,

(c) $C_{1-6}$ alkoxy group optionally substituted by 1 to 3 halogen atoms, and

(d) halogen atom;

(4) 4- to 12-membered nonaromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms,

(b) hydroxy group,

(c) $C_{1-6}$ alkoxy group optionally substituted by 1 to 3 halogen atoms,

(d) halogen atom, and

(e) oxo group;

(5) amino group optionally mono- or di-substituted by substituent(s) selected from

(a) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 substituents selected from

(i) halogen atom, and

(ii) $C_{1-6}$ alkoxy group,

(b) $C_{1-6}$ alkyl-carbonyl group optionally substituted by 1 to 3 halogen atoms,

(c) $C_{1-6}$ alkoxy-carbonyl group optionally substituted by 1 to 3

halogen atoms,

(d) $C_{1-6}$ alkylsulfonyl group optionally substituted by 1 to 3 halogen atoms,

(e) carbamoyl group optionally mono- or di-substituted by $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms,

(f) 4- to 12-membered aromatic heterocyclic group,

(g) $C_{6-14}$ aryl-carbonyl group (e.g., benzoyl),

(h) $C_{6-14}$ arylsulfonyl group (e.g., benzenesulfonyl), and

(i) $C_{7-13}$ aralkyl group (e.g., benzyl);

(6) $C_{1-6}$ alkyl-carbonyl group optionally substituted by 1 to 3 halogen atoms;

(7) $C_{1-6}$ alkoxy-carbonyl group optionally substituted by 1 to 3 substituents selected from

(a) halogen atom,

(b) $C_{1-6}$ alkoxy group, and

(c) $C_{6-14}$ aryl group;

(8) $C_{1-6}$ alkylsulfonyl group optionally substituted by 1 to 3 halogen atoms;

(9) carbamoyl group optionally mono- or di-substituted by $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms;

(10) thiocarbamoyl group optionally mono- or di-substituted by $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms;

(11) sulfamoyl group optionally mono- or di-substituted by $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms;

(12) carboxy group;

(13) hydroxy group;

(14) $C_{1-6}$ alkoxy group optionally substituted by 1 to 3 substituents selected from

(a) halogen atom,

(b) carboxy group,

(c) $C_{1-6}$ alkoxy group,

(d) $C_{3-6}$ cycloalkyl group,

(e) $C_{1-6}$ alkoxy-carbonyl group optionally substituted by 1 to 3 $C_{6-14}$ aryl groups,

(f) amino group optionally mono- or di-substituted by

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substituent(s) selected from $C_{1-6}$ alkyl group and $C_{1-6}$ alkoxy-carbonyl group,

(g) 4- to 12-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from

(i) halogen atom, and

(ii) $C_{1-6}$ alkyl group,

(h) 4- to 12-membered nonaromatic heterocyclic group optionally substituted by 1 to 3 $C_{1-6}$ alkyl groups,

(i) $C_{1-6}$ alkylsulfonyl group,

(j) $C_{1-6}$ alkylthio group, and

(k) hydroxy group;

(15) $C_{2-6}$ alkenyloxy group optionally substituted by 1 to 3 halogen atoms;

(16) $C_{7-13}$ aralkyloxy group;

(17) $C_{6-14}$ aryloxy group;

(18) $C_{1-6}$ alkyl-carbonyloxy group;

(19) 4- to 12-membered aromatic heterocyclyl-oxy group optionally substituted by 1 to 3 substituents selected from

(i) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms, and

(ii) cyano group;

(20) 4- to 12-membered non-aromatic heterocyclyl-oxy group;

(21) $C_{6-14}$ aryl-carbonyl group optionally substituted by 1 to 3 substituents selected from

(a) halogen atom, and

(b) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms;

(22) 4- to 12-membered aromatic heterocyclyl-carbonyl group optionally substituted by 1 to 3 substituents selected from $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms;

(23) 4- to 12-membered non-aromatic heterocyclyl-carbonyl group optionally substituted by 1 to 3 substituents selected from $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms;

(24) mercapto group;

(25) $C_{1-6}$ alkylthio group optionally substituted by 1to 3 substituents selected from

(a) halogen atom, and

(b) $C_{1-6}$ alkoxycarbonyl group;

(26) $C_{7-13}$ aralkylthio group;

(27) $C_{6-14}$ arylthio group;

(28) cyano group;

(29) nitro group;

(30) halogen atom;

(31) $C_{1-3}$ alkylenedioxy group;

(32) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 substituents selected from

(a) halogen atom,

(b) carboxy group,

(c) hydroxy group,

(d) $C_{1-6}$ alkoxy-carbonyl group,

(e) $C_{1-6}$ alkoxy group optionally substituted by 1 to 3 $C_{1-6}$ alkoxy groups, and

(f) amino group optionally mono- or di-substituted by $C_{1-6}$ alkyl group(s);

(33) $C_{2-6}$ alkenyl group optionally substituted by 1 to 3 substituents selected from

(a) halogen atom,

(b) carboxy group,

(c) hydroxy group,

(d) $C_{1-6}$ alkoxy-carbonyl group,

(e) $C_{1-6}$ alkoxy group, and

(f) amino group optionally mono- or di-substituted by $C_{1-6}$ alkyl group(s); and

(34) $C_{7-13}$ aralkyl group optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms,

(b) hydroxy group,

(c) $C_{1-6}$ alkoxy group, and

(d) halogen atom.

When two or more substituents are used, the respective substituents may be the same or different.

[0062]

In the present specification, the $C_{3-10}$ cycloalkyl group of the "optionally substituted $C_{3-10}$ cycloalkyl group" optionally have 1 to 5 (preferably 1 to 3) substituents at substitutable position(s). Examples of such substituent include the above-mentioned substituent group B and oxo group. When two or more substituents are used, the respective substituents may be the same or different.

[0063]

In the present specification, when the "heterocyclic group" and "5- or 6-membered heterocyclic group" of the "optionally substituted heterocyclic group" and "optionally substituted 5- or 6-membered heterocyclic group" are aromatic heterocyclic groups, the aromatic heterocyclic groups optionally have 1 to 5 (preferably 1 to 3) substituents at substitutable position(s).

Examples of such substituent include the above-mentioned substituent group B. When two or more substituents are used, the respective substituents may be the same or different.

In the present specification, when the "heterocyclic group" and "5- or 6-membered heterocyclic group" of the "optionally substituted heterocyclic group" and "optionally substituted 5- or 6-membered heterocyclic group" are nonaromatic heterocyclic groups, the nonaromatic heterocyclic groups optionally have 1 to 5 (preferably 1 to 3) substituents at substitutable position(s).

Examples of such substituent include the above-mentioned substituent group B and oxo group. When two or more substituents are used, the respective substituents may be the same or different.

[0064]

In the present specification, the 5- or 6-membered

aromatic heterocycle and 5-membered aromatic heterocycle of the "optionally substituted 5- or 6-membered aromatic heterocycle" and "optionally substituted 5-membered aromatic heterocycle" each optionally have 1 to 5 (preferably 1 to 3) substituents at substitutable position(s). Examples of such substituent include the above-mentioned substituent group B. When two or more substituents are used, the respective substituents may be the same or different.

[0065]

In the present specification, examples of the "acyl" include groups represented by the formulas: $-CO-R^A$, $-CO-OR^A$, $-S(O)_3-R^A$, $-S(O)_2-R^A$, $-S(O)-R^A$, $-CO-NR^{A'}R^{B'}$, $-CS-NR^{A'}R^{B'}$, $-S(O)_2-NR^{A'}R^{B'}$ and the like.

In the formula, $R^A$ is a hydrogen atom, an optionally substituted hydrocarbon group, or an optionally substituted heterocyclic group. $R^{A'}$ and $R^{B'}$ are each independently a hydrogen atom, an optionally substituted hydrocarbon group, or an optionally substituted heterocyclic group, or $R^{A'}$ and $R^{B'}$ form, together with the adjacent nitrogen atom, an optionally substituted nitrogen-containing non-aromatic heterocycle.

Examples of the "nitrogen-containing non-aromatic heterocycle" of the "optionally substituted nitrogen-containing non-aromatic heterocycle" formed by $R^{A'}$ and $R^{B'}$, together with the adjacent nitrogen atom, include 5- to 7-membered nitrogen-containing non-aromatic heterocycle containing, as a ring constituting atom besides carbon atom, at least one nitrogen atom, and optionally further containing 1 or 2 hetero atoms selected from oxygen atom, sulfur atom (the sulfur atom may be oxidized) and nitrogen atom. Preferable examples of such nitrogen-containing non-aromatic heterocycle include pyrrolidine, imidazolidine, pyrazolidine, piperidine, piperazine, morpholine, thiomorpholine and the like.

The nitrogen-containing non-aromatic heterocycle optionally has 1 to 5 (preferably 1 to 3) substituents at

substitutable position(s). As such substituent, the above-mentioned substituent group B and oxo group can be mentioned. When two or more substituents are used, the respective substituents may be the same or different.

[0066]

Preferable examples of the "acyl group" include

(1) formyl group;

(2) carboxy group;

(3) $C_{1-6}$ alkyl-carbonyl group optionally substituted by 1 to 3 substituents selected from

(a) halogen atom,

(b) $C_{1-6}$ alkoxy-carbonyl group,

(c) $C_{6-14}$ aryl group, and

(d) $C_{1-6}$ alkoxy group;

(4) $C_{1-6}$ alkoxy-carbonyl group optionally substituted by 1 to 3 substituents selected from

(a) halogen atom,

(b) $C_{6-14}$ aryl group, and

(c) $C_{1-6}$ alkoxy group;

(5) $C_{3-10}$ cycloalkyl-carbonyl group;

(6) $C_{6-14}$ aryl-carbonyl group optionally substituted by 1 to 3 halogen atoms;

(7) carbamoyl group optionally mono- or di-substituted by substituent(s) selected from

(a) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 substituents selected from

(i) halogen atom,

(ii) $C_{1-6}$ alkoxy-carbonyl group,

(iii) $C_{6-14}$ aryl group,

(iv) $C_{1-6}$ alkoxy group, and

(v) 4- to 12-membered aromatic heterocyclic group,

(b) $C_{3-10}$ cycloalkyl group,

(c) $C_{6-14}$ aryl group optionally substituted by 1 to 3 substituents selected from

(i) halogen atom,

(ii) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms, and

(iii) $C_{1-6}$ alkoxy group, and

(d) 4- to 12-membered aromatic heterocyclic group;

(8) $C_{1-6}$ alkylsulfonyl group optionally substituted by 1 to 3 substituents selected from

(a) halogen atom, and

(b) $C_{6-14}$ aryl group;

(9) $C_{6-14}$ arylsulfonyl group optionally substituted by 1 to 3 halogen atoms;

(10) sulfamoyl group optionally mono- or di-substituted by substituent(s) selected from

(a) halogen atom, and

(b) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 substituents selected from 4- to 12-membered nonaromatic heterocyclic group optionally substituted by oxo group;

(11) thiocarbamoyl group optionally mono- or di-substituted by substituent(s) selected from $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms;

(12) 4- to 12-membered aromatic heterocyclyl-carbonyl group optionally substituted by 1 to 3 substituents selected from $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms;

(13) 4- to 12-membered non-aromatic heterocyclyl-carbonyl group optionally substituted by 1 to 3 substituents selected from $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms;

and the like.

[0067]

Compound (I) is explained.

Ring A is an optionally substituted benzene ring or optionally substituted 5- or 6-membered aromatic heterocycle.

The 5- or 6-membered aromatic heterocycle for ring A is preferably pyridine.

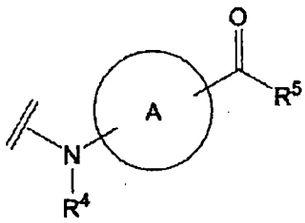
The "benzene ring" or "5- or 6-membered aromatic heterocycle" of the "optionally substituted benzene ring or

optionally substituted 5- or 6-membered aromatic heterocycle" for ring A optionally further has 1 to 4 substituents at substitutable position(s) besides "-$NR^4$- group" and "-CO-$R^5$ group".

The ring A is preferably a benzene ring or 5- or 6-membered aromatic heterocycle (e.g., pyridine), more preferably benzene or 6-membered aromatic heterocycle (e.g., pyridine), particularly preferably a benzene ring, without a substituent other than the "-$NR^4$- group" and "-CO-$R^5$ group".

When ring A is benzene or 6-membered aromatic heterocycle, the following part containing ring A in the formula (I):

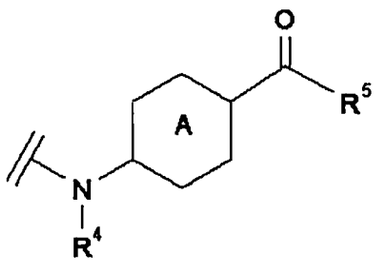
[0068]




[0069]

is preferably

[0070]




[0071]

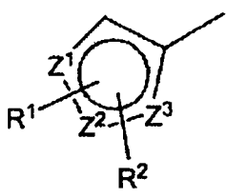
wherein the symbols other than ring A are as defined above.

[0072]

Ring B is pyrazole.

Specific examples of pyrazole for ring B include

[0073]

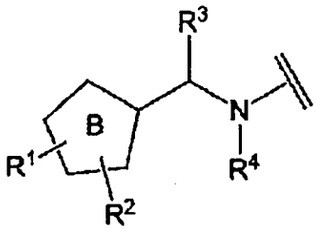


[0074]

wherein $Z^1$, $Z^2$ and $Z^3$ are: 1) $Z^1$ and $Z^2$ are nitrogen atoms and $Z^3$ is a carbon atom, or 2) $Z^2$ and $Z^3$ are nitrogen atoms and $Z^1$ is a carbon atom; $R^1$ and $R^2$ are as defined above, and these groups are substituted at any substitutable position of a pyrazole ring.

The following part containing ring B in the formula (I):

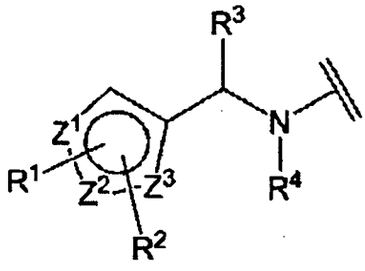
[0075]




[0076]

is specifically

[0077]

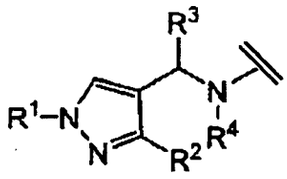



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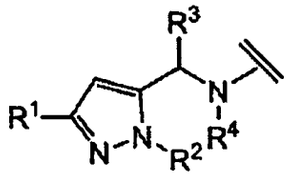
[0078]

preferably

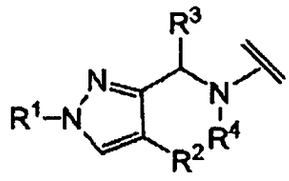
[0079]




、




or

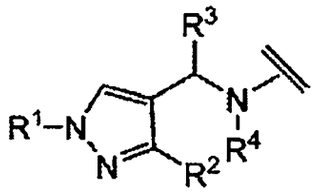



,

[0080]

more preferably

[0081]



[0082]

wherein each symbol in the formula is as defined above.

[0083]

$R^1$ and $R^2$ are each independently an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted hydroxy group or acyl.

[0084]

$R^1$ is preferably

(1) optionally substituted $C_{1-6}$ alkyl group (e.g., methyl, 1,1-dimethylpropyl),

(2) optionally substituted $C_{6-14}$ aryl group (e.g., phenyl), or

(3) optionally substituted 5- or 6-membered aromatic heterocyclic group (e.g., pyridyl),

more preferably

(1) $C_{1-6}$ alkyl group (e.g., methyl, 1,1-dimethylpropyl) optionally substituted by 1 to 3 substituents selected from

(a) halogen atom (e.g., fluorine),

(b) $C_{6-14}$ aryl group (e.g., phenyl), and

(c) $C_{1-6}$ alkoxy group (e.g., methoxy),

(2) $C_{6-14}$ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from

(a) halogen atom (e.g., fluorine, chlorine),

(b) $C_{1-6}$ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine), and

(c) $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine), or

(3) 5- or 6-membered aromatic heterocyclic group (e.g., pyridyl) optionally substituted by 1 to 3 substituents selected from

(a) halogen atom (e.g., fluorine, chlorine),

(b) $C_{1-6}$ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine), and

(c) $C_{1-6}$ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine).

[0085]

$R^2$ is preferably

(1) optionally substituted $C_{1-6}$ alkyl group (e.g., methyl, ethyl, t-butyl, n-propyl, isopropyl),

(2) hydroxy group substituted by optionally substituted $C_{1-6}$ alkyl group, namely, optionally substituted $C_{1-6}$ alkoxy group (e.g., methoxy, isopropoxy), or

(3) optionally substituted $C_{3-10}$ cycloalkyl group (e.g., cyclopropyl, cyclohexyl), more preferably

(1) $C_{1-6}$ alkyl group (e.g., methyl, ethyl, t-butyl, n-propyl, isopropyl) optionally substituted by 1 to 3 substituents selected from

(a) halogen atom (e.g., fluorine, chlorine),

(b) $C_{6-14}$ aryl group (e.g., phenyl),

(c) $C_{1-6}$ alkoxy group (e.g., methoxy), and

(d) 4- to 12-membered nonaromatic heterocyclic group (e.g., morpholino),

(2) $C_{1-6}$ alkoxy group (e.g., methoxy, isopropoxy) optionally substituted by 1 to 3 substituents selected from

(a) halogen atom (e.g., fluorine, chlorine),

(b) $C_{6-14}$ aryl group (e.g., phenyl), and

(c) $C_{1-6}$ alkoxy group (e.g., methoxy), or

(3) $C_{3-10}$ cycloalkyl group (e.g., cyclopropyl, cyclohexyl).

[0086]

$R^3$ is an optionally substituted $C_{1-6}$ alkyl group, optionally substituted $C_{3-10}$ cycloalkyl group, optionally substituted $C_{6-14}$ aryl group or optionally substituted heterocyclic group.

[0087]

The "optionally substituted heterocyclic group" for $R^3$ is preferably an optionally substituted 5- or 6-membered

heterocyclic group.

[0088]

$R^3$ is preferably

(1) optionally substituted $C_{1-6}$ alkyl group (preferably, branched $C_{1-6}$ alkyl group (e.g., isopropyl, isobutyl, 1-ethylpropyl)),

(2) optionally substituted $C_{3-10}$ cycloalkyl group (e.g., cyclopentyl, cyclohexyl), or

(3) optionally substituted 5- or 6-membered heterocyclic group (e.g., pyridyl, piperidyl, tetrahydrothiopyranyl, 1-oxidotetrahydrothiopyranyl, 1,1-dioxidotetrahydrothiopyranyl),

more preferably

(1) $C_{1-6}$ alkyl group (preferably, branched $C_{1-6}$ alkyl group (e.g., isopropyl, isobutyl, 1-ethylpropyl)) optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy, propoxy) optionally substituted by 1 to 3 $C_{1-6}$ alkoxy groups (e.g., methoxy),

(b) $C_{6-14}$ aryloxy group (e.g., phenyloxy),

(c) $C_{7-13}$ aralkyloxy group (e.g., benzyloxy),

(d) amino group optionally mono- or di-substituted by $C_{1-6}$ alkyl group (e.g., methyl),

(e) 4- to 12-membered nonaromatic heterocyclic group (e.g., piperidyl, morphonyl),

(f) $C_{1-6}$ alkylsulfonyl group (e.g., methylsulfonyl, isopropylsulfonyl), and

(g) $C_{6-14}$ arylsulfonyl group (e.g., benzenesulfonyl),

(2) $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl), or

(3) 5- or 6-membered heterocyclic group (e.g., pyridyl, piperidyl, tetrahydrothiopyranyl, 1-oxidotetrahydrothiopyranyl, 1,1-dioxidotetrahydrothiopyranyl) optionally substituted by 1 to 3 $C_{6-14}$ aryl groups (e.g., phenyl).

[0089]

$R^4$ is a hydrogen atom or a $C_{1-6}$ alkyl group.

$R^4$ is preferably a hydrogen atom.

[0090]

$R^5$ is a group represented by $-(CH_2)_3-COOR^{11}$ or $-NR^6-CR^7R^8-CR^9R^{10}-COOR^{11}$ wherein $R^6$, $R^7$, $R^8$, $R^9$ and $R^{11}$ are each independently a hydrogen atom or a $C_{1-6}$ alkyl group, and $R^{10}$ is a hydrogen atom, a $C_{1-6}$ alkyl group or a hydroxy group.

$R^6$ is preferably a hydrogen atom or methyl, more preferably a hydrogen atom.

$R^7$ is preferably a hydrogen atom.

$R^8$ is preferably a hydrogen atom.

$R^9$ is preferably a hydrogen atom, methyl or ethyl, more preferably a hydrogen atom.

$R^{10}$ is preferably a hydrogen atom, methyl or ethyl, more preferably a hydrogen atom.

$R^{11}$ is preferably a hydrogen atom, methyl or ethyl, more preferably a hydrogen atom.

$R^5$ is preferably $-NR^6-CR^7R^8-CR^9R^{10}-COOR^{11}$.

[0091]

Of compounds (I), a compound wherein

$R^1$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{6-14}$ aryl group, or an optionally substituted 5- or 6-membered aromatic heterocyclic group;

$R^2$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{1-6}$ alkoxy group, or an optionally substituted $C_{3-10}$ cycloalkyl group;

$R^3$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{3-10}$ cycloalkyl group, or an optionally substituted 5- or 6-membered heterocyclic group;

$R^4$ is a hydrogen atom;

$R^5$ is $-(CH_2)_3-COOR^{11}$ or $-NR^6-CH_2-CR^9R^{10}-COOR^{11}$;

$R^6$ is a hydrogen atom or methyl;

$R^9$ is a hydrogen atom, methyl or ethyl;

$R^{10}$ is a hydrogen atom, methyl or ethyl; and

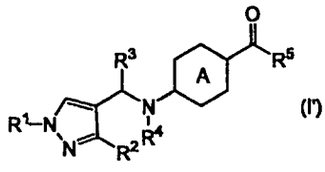
$R^{11}$ is a hydrogen atom, methyl or ethyl is preferable.

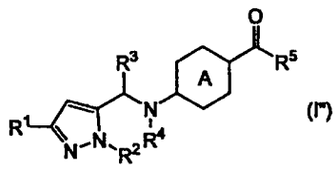
[0092]

When ring A is a benzene ring or 6-membered aromatic

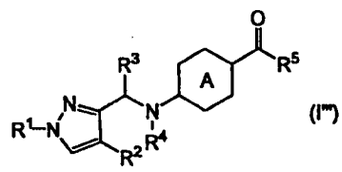
heterocycle, specific preferable examples of the formula (I) include the following formulas (I'), (I") and (I"')

[0093]


(I')


(I")

or


(I"')

[0094]

wherein each symbol other than ring A is as defined above; compound represented by the above-mentioned formulas (I'), (I") and (I"') and salts thereof are encompassed in compound (I).

The formula (I) is more preferably the formula (I').

[0095]

Preferable examples of compound (I) include the following compounds.

(compound A)

In the formula (I), a compound wherein ring A is a benzene ring or 5- or 6-membered aromatic heterocycle (preferably, pyridine);

ring B is pyrazole;

$R^1$ is

(1) optionally substituted $C_{1-6}$ alkyl group (e.g., methyl, 1,1-dimethylpropyl),

(2) optionally substituted $C_{6-14}$ aryl group (e.g., phenyl), or

(3) optionally substituted 5- or 6-membered aromatic heterocyclic group (e.g., pyridyl);

$R^2$ is

(1) optionally substituted $C_{1-6}$ alkyl group (e.g., methyl, ethyl, t-butyl, n-propyl, isopropyl),

(2) optionally substituted $C_{1-6}$ alkoxy group (e.g., methoxy, isopropoxy), or

(3) optionally substituted $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl);

$R^3$ is

(1) optionally substituted $C_{1-6}$ alkyl group (preferably, branched $C_{1-6}$ alkyl group (e.g., isopropyl, isobutyl, 1-ethylpropyl)),

(2) optionally substituted $C_{3-10}$ cycloalkyl group (e.g., cyclopropyl, cyclohexyl), or

(3) optionally substituted 5- or 6-membered heterocyclic group (e.g., pyridyl, piperidyl, tetrahydrothiopyranyl, 1-oxidotetrahydrothiopyranyl, 1,1-dioxidotetrahydrothiopyranyl);

$R^4$ is a hydrogen atom; and

$R^5$ is $-(CH_2)_3-COOR^{11}$ or $-NR^6-(CH_2)_2-COOR^{11}$ (preferably, $-NR^6-(CH_2)_2-COOR^{11}$)

wherein $R^6$ is a hydrogen atom or methyl (preferably, a hydrogen atom), and

$R^{11}$ is a hydrogen atom, methyl or ethyl (preferably, a hydrogen atom);

or a salt thereof.

[0096]

(compound A-1)

A compound of the formula (I), which is a compound of the formula (I') or (I") (preferably, formula (I')),

wherein, ring A is a benzene ring or 6-membered aromatic heterocycle (e.g., pyridine);

$R^1$ is

(1) $C_{1-6}$ alkyl group (e.g., methyl, 1,1-dimethylpropyl) optionally substituted by 1 to 3 substituents selected from

(a) halogen atom (e.g., fluorine),

(b) $C_{6-14}$ aryl group (e.g., phenyl), and

(c) $C_{1-6}$ alkoxy group (e.g., methoxy),

(2) $C_{6-14}$ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from

(a) halogen atom (e.g., fluorine, chlorine),

(b) $C_{1-6}$ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine), and

(c) $C_{1-6}$ alkoxy group (e.g., methoxy) optionally substituted by

1 to 3 halogen atoms (e.g., fluorine), or

(3) 5- or 6-membered aromatic heterocyclic group (e.g., pyridyl) optionally substituted by 1 to 3 substituents selected from

(a) halogen atom (e.g., fluorine, chlorine),

(b) $C_{1-6}$ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine), and

(c) $C_{1-6}$ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine);

$R^2$ is

(1) $C_{1-6}$ alkyl group (e.g., methyl, ethyl, t-butyl, n-propyl, isopropyl) optionally substituted by 1 to 3 substituents selected from

(a) halogen atom (e.g., fluorine, chlorine),

(b) $C_{6-14}$ aryl group (e.g., phenyl), and

(c) $C_{1-6}$ alkoxy group (e.g., methoxy),

(2) $C_{1-6}$ alkoxy group (e.g., methoxy, isopropoxy) optionally substituted by 1 to 3 substituents selected from

(a) halogen atom (e.g., fluorine, chlorine),

(b) $C_{6-14}$ aryl group (e.g., phenyl), and

(c) $C_{1-6}$ alkoxy group (e.g., methoxy), or

(3) $C_{3-10}$ cycloalkyl group (e.g., cyclopropyl, cyclohexyl);

$R^3$ is

(1) $C_{1-6}$ alkyl group (preferably, branched $C_{1-6}$ alkyl group (e.g., isobutyl, 1-ethylpropyl)) optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy, propoxy) optionally substituted by 1 to 3 $C_{1-6}$ alkoxy groups (e.g., methoxy),

(b) $C_{6-14}$ aryloxy group (e.g., phenyloxy),

(c) $C_{7-13}$ aralkyloxy group (e.g., benzyloxy),

(d) amino group optionally mono- or di-substituted by $C_{1-6}$ alkyl group (e.g., methyl),

(e) 4- to 12-membered nonaromatic heterocyclic group (e.g., piperidyl, morphonyl),

(f) $C_{1-6}$ alkylsulfonyl group (e.g., methylsulfonyl, isopropylsulfonyl), and

(g) $C_{6-14}$ arylsulfonyl group (e.g., benzenesulfonyl),

(2) $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl), or

(3) 5- or 6-membered heterocyclic group (e.g., pyridyl, piperidyl, tetrahydrothiopyranyl, 1-oxidotetrahydrothiopyranyl, 1,1-dioxidotetrahydrothiopyranyl) optionally substituted by 1 to 3 $C_{6-14}$ aryl groups (e.g., phenyl);

$R^4$ is a hydrogen atom; and

$R^5$ is $-(CH_2)_3-COOH$ or $-NR^6-(CH_2)_2-COOH$, preferably $-NR^6-(CH_2)_2-COOH$

wherein $R^6$ is a hydrogen atom or methyl (preferably, hydrogen atom));

or a salt thereof.

[0097]

(compound A-2)

A compound of the formula (I), which is a compound of the formula (I'), (I") or (I"') (preferably, formula (I')), wherein, ring A is a benzene ring or 6-membered aromatic heterocycle (e.g., pyridine);

$R^1$ is

(1) $C_{1-6}$ alkyl group (e.g., methyl, 1,1-dimethylpropyl) optionally substituted by 1 to 3 substituents selected from

(a) halogen atom (e.g., fluorine),

(b) $C_{6-14}$ aryl group (e.g., phenyl), and

(c) $C_{1-6}$ alkoxy group (e.g., methoxy),

(2) $C_{6-14}$ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from

(a) halogen atom (e.g., fluorine, chlorine),

(b) $C_{1-6}$ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine), and

(c) $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine),

or

(3) 5- or 6-membered aromatic heterocyclic group (e.g.,

pyridyl) optionally substituted by 1 to 3 substituents selected from

(a) halogen atom (e.g., fluorine, chlorine),

(b) $C_{1-6}$ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine) and

(c) $C_{1-6}$ alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine);

$R^2$ is

(1) $C_{1-6}$ alkyl group (e.g., methyl, ethyl, t-butyl, n-propyl, isopropyl) optionally substituted by 1 to 3 substituents selected from

(a) halogen atom (e.g., fluorine, chlorine),

(b) $C_{6-14}$ aryl group (e.g., phenyl),

(c) $C_{1-6}$ alkoxy group (e.g., methoxy), and

(d) 4- to 12-membered nonaromatic heterocyclic group (e.g., morpholino)

(2) $C_{1-6}$ alkoxy group (e.g., methoxy, isopropoxy) optionally substituted by 1 to 3 substituents selected from

(a) halogen atom (e.g., fluorine, chlorine),

(b) $C_{6-14}$ aryl group (e.g., phenyl), and

(c) $C_{1-6}$ alkoxy group (e.g., methoxy), or

(3) $C_{3-10}$ cycloalkyl group (e.g., cyclopropyl, cyclohexyl);

$R^3$ is

(1) $C_{1-6}$ alkyl group(preferably, branched $C_{1-6}$ alkyl group (e.g., isobutyl, 1-ethylpropyl)) optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy, propoxy) optionally substituted by 1 to 3 $C_{1-6}$ alkoxy groups (e.g., methoxy),

(b) $C_{6-14}$ aryloxy group (e.g., phenyloxy),

(c) $C_{7-13}$ aralkyloxy group (e.g., benzyloxy),

(d) amino group optionally mono- or di-substituted by $C_{1-6}$ alkyl group (e.g., methyl),

(e) 4- to 12-membered nonaromatic heterocyclic group (e.g., piperidyl, morphonyl),

(f) $C_{1-6}$ alkylsulfonyl group (e.g., methylsulfonyl, isopropylsulfonyl), and

(g) $C_{6-14}$ arylsulfonyl group (e.g., benzenesulfonyl),

(2) $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl), or

(3) 5- or 6-membered heterocyclic group (e.g., pyridyl, piperidyl, tetrahydrothiopyranyl, 1-oxidotetrahydrothiopyranyl, 1,1-dioxidotetrahydrothiopyranyl) optionally substituted by 1 to 3 $C_{6-14}$ aryl groups (e.g., phenyl);

$R^4$ is a hydrogen atom; and

$R^5$ is $-(CH_2)_3-COOR^{11}$ or $-NR^6-CH_2-CR^9R^{10}-COOR^{11}$, preferably $-NR^6-CH_2-CR^9R^{10}-COOR^{11}$

wherein $R^6$ is a hydrogen atom or methyl (preferably, a hydrogen atom),

$R^9$ is a hydrogen atom, methyl or ethyl (preferably, a hydrogen atom),

$R^{10}$ is a hydrogen atom, methyl or ethyl (preferably, a hydrogen atom),

$R^{11}$ is a hydrogen atom, methyl or ethyl (preferably, a hydrogen atom);

or a salt thereof.

[0098]

(compound A-3)

3-[({4-[(Cyclohexyl{3-methyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid or a salt thereof (Example 1);

3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid or a salt thereof (Example 70); or

3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid or a salt thereof (Example 76).

[0099]

Compound (IA) is explained in the following.

[0100]

The ring AA is an optionally substituted benzene ring, or an optionally substituted 5- or 6-membered aromatic heterocycle.

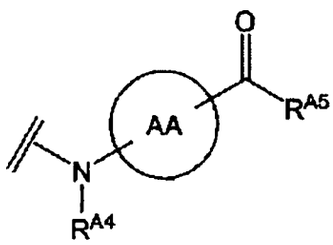
The 5- or 6-membered aromatic heterocycle for ring AA is preferably pyridine.

The "benzene ring" or "5- or 6-membered aromatic heterocycle" of the "optionally substituted benzene ring, or an optionally substituted 5- or 6-membered aromatic heterocycle" for ring AA optionally further has 1 to 4 substituents at substitutable position(s) besides the "-$NR^{A4}$- group" and "-CO-$R^{A5}$ group".

The ring AA is preferably a benzene ring or 5- or 6-membered aromatic heterocycle (e.g., pyridine), more preferably a benzene ring or 6-membered aromatic heterocycle (e.g., pyridine), particularly preferably a benzene ring, which does not have a substituent besides the "-$NR^{A4}$- group" and the "-CO-$R^{A5}$ group".

When ring AA is a benzene ring or 6-membered aromatic heterocycle, the following part containing ring AA in the formula (IA)

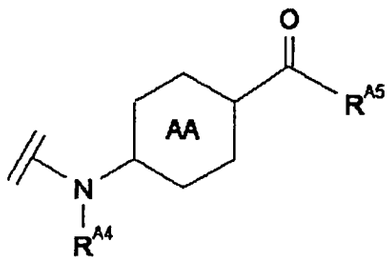
[0101]




[0102]

is preferably

[0103]




[0104]

wherein each symbol other than ring AA is as defined above.

[0105]

Ring AB is an optionally substituted 5-membered aromatic heterocycle.

The 5-membered aromatic heterocycle for ring AB is preferably pyrrole, thiophene, furan, imidazole or pyrazole.

The "5-membered aromatic heterocycle" of the "optionally substituted 5-membered aromatic heterocycle" for ring AB optionally further has 1 or 2 substituents at substitutable position(s) besides the "$-CH(R^{A3})-$ group".

Ring AB is preferably 5-membered aromatic heterocycle (e.g., pyrrole, thiophene, furan, imidazole, pyrazole, pyrrole) optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 $C_{1-6}$ alkoxy groups (e.g., methoxy),

(b) $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl),

(c) $C_{6-14}$ aryl group (e.g., phenyl) optionally having 1 to 3 $C_{1-6}$ alkyl groups (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine),

(d) cyano group,

(e) $C_{1-6}$ alkoxy group (e.g., methoxy), and

(f) halogen atom (e.g., bromine atom).

[0106]

Ring AC is an optionally substituted benzene ring or optionally substituted 5- or 6-membered aromatic heterocycle.

The 5- or 6-membered aromatic heterocycle for ring AC is preferably pyridine.

The "benzene ring" or "5- or 6-membered aromatic heterocycle" of the "optionally substituted benzene ring or optionally substituted 5- or 6-membered aromatic heterocycle" for ring AC optionally further has 1 to 4 substituents at substitutable position(s).

Ring AC is preferably

(1) a benzene ring optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine),

(b) $C_{3-10}$ cycloalkyl group (e.g., cyclopropyl, cyclohexyl),

(c) $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy, propoxy, isobutoxy) optionally substituted by 1 to 3 substituents selected from

(i) $C_{1-6}$ alkoxy group (e.g., methoxy),

(ii) $C_{3-6}$ cycloalkyl group (e.g., cyclopropyl),

(iii) 4- to 12-membered aromatic heterocyclic group (e.g., oxazolyl, isoxazolyl, pyridyl) optionally substituted by 1 to 3 substituents selected from

(i') halogen atom (e.g., fluorine, chlorine), and

(ii') $C_{1-6}$ alkyl group (e.g., methyl),

(iv) 4- to 12-membered nonaromatic heterocyclic group (e.g., oxetanyl, tetrahydrofuryl) optionally substituted by 1 to 3 $C_{1-6}$ alkyl groups (e.g., methyl),

(v) $C_{1-6}$ alkylsulfonyl group (e.g., methylsulfonyl),

(vi) $C_{1-6}$ alkylthio group (e.g., methylthio), and

(vii) hydroxy group,

(d) halogen atom (e.g., fluorine, chlorine),

(e) $C_{7-13}$ aralkyloxy group (e.g., benzyloxy),

(f) 4- to 12-membered non-aromatic heterocyclyl-oxy group (e.g., tetrahydropyranyloxy, tetrahydrothiopyranyloxy, 1,1-dioxidotetrahydrothiopyranyloxy),

(g) 4- to 12-membered aromatic heterocyclyl-oxy group (e.g., pyridyloxy) optionally substituted by 1 to 3 substituents selected from

(i) $C_{1-6}$ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine), and

(ii) cyano group,

(h) $C_{6-14}$ aryl group (e.g., phenyl),

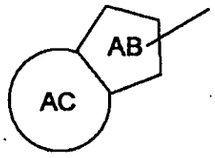
(i) 4- to 12-membered aromatic heterocyclic group (e.g.,

oxazolyl, isoxazolyl, pyrazolyl, pyridyl) optionally substituted by 1 to 3 substituents selected from
(i) $C_{1-6}$ alkyl group (e.g., methyl), and
(ii) $C_{1-6}$ alkoxy group (e.g., methoxy),
(j) 4- to 12-membered nonaromatic heterocyclic group (e.g., morpholino, thiomorpholino),
(k) $C_{7-13}$ aralkyl group (e.g., benzyl),
(l) cyano group,
(m) amino group optionally mono- or di-substituted by substituent(s) selected from
(i) $C_{1-6}$ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 $C_{1-6}$ alkoxy groups (e.g., methoxy),
(ii) $C_{1-6}$ alkyl-carbonyl group (e.g., acetyl),
(iii) $C_{1-6}$ alkylsulfonyl group (e.g., methylsulfonyl),
(iv) carbamoyl group optionally mono- or di-substituted by $C_{1-6}$ alkyl group (e.g., ethyl),
(v) $C_{6-14}$ aryl-carbonyl group (e.g., benzoyl),
(vi) $C_{6-14}$ arylsulfonyl group (e.g., benzenesulfonyl), and
(vii) $C_{7-13}$ aralkyl group (e.g., benzyl), and
(n) $C_{6-14}$ arylsulfonyl group (e.g., benzenesulfonyl), or
(2) 5- or 6-membered aromatic heterocycle (e.g., pyridine) optionally substituted by 1 to 3 substituents selected from
(a) $C_{1-6}$ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine),
(b) $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl),
(c) $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 substituents selected from
(i) $C_{1-6}$ alkoxy group (e.g., methoxy), and
(ii) $C_{3-6}$ cycloalkyl group (e.g., cyclopropyl),
(d) halogen atom (e.g., fluorine, chlorine, bromine),
(e) $C_{7-13}$ aralkyloxy group (e.g., benzyloxy), and
(f) 4- to 12-membered non-aromatic heterocyclyl-oxy group (e.g., tetrahydropyranyloxy).

[0107]

In the formula (IA), the part represented by

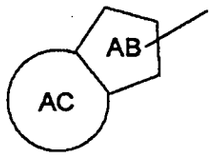
[0108]




[0109]

is a group derived from a bicyclic ring formed by ring AB and ring AC having one side of each ring in common (i.e., condensed). Here, the side of ring AB and the side of ring AC involved in the formation of the bicyclic ring are bonded at the same multiplicity. For example, when, in the formula (IA), the part represented by

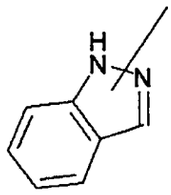
[0110]




[0111]

is a group represented by

[0112]




,

[0113]

ring AB is "pyrazole" and ring AC is "benzene".

In the fused ring formed by ring AC and ring AB, the "-$CH(R^{A3})$- group" is present at any bondable position on ring AB.

[0114]

$R^{A3}$ is an optionally substituted $C_{1-6}$ alkyl group, optionally substituted $C_{3-10}$ cycloalkyl group, optionally substituted $C_{6-14}$ aryl group or optionally substituted heterocyclic group.

[0115]

The "optionally substituted heterocyclic group" for $R^{A3}$ is preferably an optionally substituted 5- or 6-membered heterocyclic group.

[0116]

$R^{A3}$ is preferably

(1) optionally substituted $C_{1-6}$ alkyl group (preferably, branched $C_{1-6}$ alkyl group (e.g., isopropyl, isobutyl, 1-ethylpropyl)),

(2) optionally substituted $C_{3-10}$ cycloalkyl group (e.g., cyclopentyl, cyclohexyl), or

(3) optionally substituted 5- or 6-membered heterocyclic group (e.g., pyridyl, piperidyl, tetrahydrothiopyranyl, 1-oxidotetrahydrothiopyranyl, 1,1-dioxidotetrahydrothiopyranyl),

more preferably

(1) $C_{1-6}$ alkyl group (preferably, methyl, ethyl, butyl, hexyl, branched $C_{1-6}$ alkyl group (e.g., isopropyl, isobutyl, 1-ethylpropyl)) optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy, propoxy) optionally substituted by 1 to 3 $C_{1-6}$ alkoxy groups (e.g., methoxy),

(b) $C_{6-14}$ aryloxy group (e.g., phenyloxy),

(c) $C_{7-13}$ aralkyloxy group (e.g., benzyloxy),

(d) amino group optionally mono- or di-substituted by $C_{1-6}$ alkyl group (e.g., methyl),

(e) 4- to 12-membered nonaromatic heterocyclic group (e.g., piperidyl, morphonyl),

(f) $C_{1-6}$ alkylsulfonyl group (e.g., methylsulfonyl, isopropylsulfonyl),

(g) $C_{6-14}$ arylsulfonyl group (e.g., benzenesulfonyl), and

(h) $C_{1-6}$ alkylthio group (e.g., methylthio),

(2) $C_{3-10}$ cycloalkyl group (e.g., cyclopentyl, cyclohexyl),

(3) 5- or 6-membered heterocyclic group (e.g., pyridyl, piperidyl, tetrahydrothiopyranyl, 1-oxidotetrahydrothiopyranyl, 1,1-dioxidotetrahydrothiopyranyl) optionally substituted by 1 to 3 $C_{6-14}$ aryl groups (e.g., phenyl), or

(4) $C_{6-14}$ aryl (e.g., phenyl).

[0117]

$R^{A4}$ is a hydrogen atom or a $C_{1-6}$ alkyl group.

$R^{A4}$ is preferably a hydrogen atom.

[0118]

$R^{A5}$ is a group represented by $-(CH_2)_3-COOR^{A11}$ or $-NR^{A6}-CR^{A7}R^{A8}-CR^{A9}R^{A10}-COOR^{A11}$, wherein $R^{A6}$, $R^{A7}$, $R^{A8}$, $R^{A9}$ and $R^{A11}$ are each independently a hydrogen atom or a $C_{1-6}$ alkyl group, and $R^{A10}$ is a hydrogen atom, a $C_{1-6}$ alkyl group or a hydroxy group.

$R^{A6}$ is preferably a hydrogen atom or methyl, more preferably a hydrogen atom.

$R^{A7}$ is preferably a hydrogen atom.

$R^{A8}$ is preferably a hydrogen atom.

$R^{A9}$ is preferably a hydrogen atom.

$R^{A10}$ is preferably a hydrogen atom.

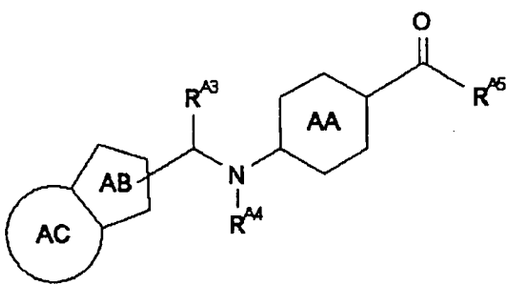
$R^{A11}$ is preferably a hydrogen atom, methyl or ethyl, more preferably a hydrogen atom.

$R^{A5}$ is preferably $-NR^{A6}-CR^{A7}R^{A8}-CR^{A9}R^{A10}-COOR^{A11}$.

[0119]

When ring AA is a benzene ring or 6-membered aromatic heterocycle, specific preferable examples of the formula (I) include the following formula (IA')

[0120]




(IA')

[0121]

(wherein each symbol other than ring AA is as defined above).

A compound represented by the above-mentioned formula (IA') and a salt thereof are encompassed in compound (IA).

Of the compounds represented by the above-mentioned formula (IA'), a compound wherein

$R^{A3}$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{3-10}$ cycloalkyl group, or an optionally substituted

5- or 6-membered heterocyclic group;

$R^{A4}$ is a hydrogen atom;

$R^{A5}$ is $-(CH_2)_3-COOR^{A11}$ or $-NR^{A6}-(CH_2)_2-COOR^{A11}$;

$R^{A6}$ is a hydrogen atom or methyl; and

$R^{A11}$ is a hydrogen atom, methyl or ethyl is preferable.

[0122]

Preferable examples of compound (IA) include the following compounds.

[0123]

(compound AA)

In the formula (IA), a compound wherein

ring AA is a benzene ring or 5- or 6-membered aromatic heterocycle (e.g., pyridine);

ring AB is an optionally substituted 5-membered aromatic heterocycle (e.g., pyrrole, thiophene, furan, imidazole, pyrazole);

ring AC is an optionally substituted benzene ring, or an optionally substituted 5- or 6-membered aromatic heterocycle (e.g., pyridine);

$R^{A3}$ is

(1) optionally substituted $C_{1-6}$ alkyl group (preferably, branched $C_{1-6}$ alkyl group (e.g., isopropyl, isobutyl, 1-ethylpropyl)),

(2) optionally substituted $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl), or

(3) optionally substituted 5- or 6-membered heterocyclic group (e.g., pyridyl, piperidyl, tetrahydrothiopyranyl, 1-oxidotetrahydrothiopyranyl, 1,1-dioxidotetrahydrothiopyranyl);

$R^{A4}$ is a hydrogen atom; and

$R^{A5}$ is $-(CH_2)_3-COOR^{A11}$ or $-NR^{A6}-(CH_2)_2-COOR^{A11}$, preferably $-NR^{A6}-(CH_2)_2-COOR^{A11}$

wherein $R^{A6}$ is a hydrogen atom or methyl (preferably, a hydrogen atom),

$R^{A11}$ is a hydrogen atom, methyl or ethyl (preferably, a hydrogen atom);

or a salt thereof.

[0124]

(compound AA-1)

A compound of the formula (IA), which is a compound of the formula (IA'), wherein

ring AA is a benzene ring or 6-membered aromatic heterocycle (e.g., pyridine);

ring AB is 5-membered aromatic heterocycle (e.g., thiophene, furan, imidazole, pyrazole) optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group (e.g., methyl, ethyl),

(b) $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl), and

(c) $C_{6-14}$ aryl group (e.g., phenyl);

ring AC is

(1) a benzene ring optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine),

(b) $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl),

(c) $C_{1-6}$ alkoxy group (e.g., methoxy), and

(d) halogen atom (e.g., fluorine), or

(2) 5- or 6-membered aromatic heterocycle (e.g., pyridine) optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine),

(b) $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl),

(c) $C_{1-6}$ alkoxy group (e.g., methoxy), and

(d) halogen atom (e.g., fluorine);

$R^{A3}$ is

(1) a $C_{1-6}$ alkyl group (preferably, branched $C_{1-6}$ alkyl group (e.g., isobutyl, 1-ethylpropyl)) optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy, propoxy) optionally substituted by 1 to 3 $C_{1-6}$ alkoxy groups (e.g., methoxy),

(b) $C_{6-14}$ aryloxy group (e.g., phenyloxy),

(c) $C_{7-13}$ aralkyloxy group (e.g., benzyloxy),

(d) amino group optionally mono- or di-substituted by $C_{1-6}$ alkyl group (e.g., methyl),

(e) 4- to 12-membered nonaromatic heterocyclic group (e.g., piperidyl, morphonyl),

(f) $C_{1-6}$ alkylsulfonyl group (e.g., methylsulfonyl, isopropylsulfonyl), and

(g) $C_{6-14}$ arylsulfonyl group (e.g., benzenesulfonyl),

(2) a $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl), or

(3) 5- or 6-membered heterocyclic group (e.g., pyridyl, piperidyl, tetrahydrothiopyranyl, 1-oxidotetrahydrothiopyranyl, 1,1-dioxidotetrahydrothiopyranyl) optionally substituted by 1 to 3 $C_{6-14}$ aryl groups (e.g., phenyl);

$R^{A4}$ is a hydrogen atom; and

$R^{A5}$ is $-(CH_2)_3-COOH$ or $-NR^{A6}-(CH_2)_2-COOH$, preferably $-NR^{A6}-(CH_2)_2-COOH$

wherein $R^{A6}$ is a hydrogen atom or methyl (preferably, a hydrogen atom);

or a salt thereof.

[0125]

(compound AA-2)

A compound of the formula (IA), which is a compound of the formula (IA'), wherein

ring AA is a benzene ring or 6-membered aromatic heterocycle (e.g., pyridine);

ring AB is 5-membered aromatic heterocycle (e.g., thiophene, furan, imidazole, pyrazole) optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 $C_{1-6}$ alkoxy groups (e.g., methoxy),

(b) $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl), and

(c) $C_{6-14}$ aryl group (e.g., phenyl);

ring AC is

(1) a benzene ring optionally substituted by 1 to 3

substituents selected from

(a) $C_{1-6}$ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine),

(b) $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl),

(c) $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 substituents selected from

(i) $C_{1-6}$ alkoxy group (e.g., methoxy), and

(ii) $C_{3-6}$ cycloalkyl group (e.g., cyclopropyl),

(d) halogen atom (e.g., fluorine),

(e) $C_{7-13}$ aralkyloxy group (e.g., benzyloxy), and

(f) 4- to 12-membered non-aromatic heterocyclyl-oxy group (e.g., tetrahydropyranyloxy), or

(2) 5- or 6-membered aromatic heterocycle (e.g., pyridine) optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine),

(b) $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl),

(c) $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 substituents selected from

(i) $C_{1-6}$ alkoxy group (e.g., methoxy), and

(ii) $C_{3-6}$ cycloalkyl group (e.g., cyclopropyl),

(d) halogen atom (e.g., fluorine),

(e) $C_{7-13}$ aralkyloxy group (e.g., benzyloxy), and

(f) 4- to 12-membered non-aromatic heterocyclyl-oxy group (e.g., tetrahydropyranyloxy);

$R^{A3}$ is

(1) $C_{1-6}$ alkyl group (preferably, branched $C_{1-6}$ alkyl group (e.g., isopropyl, isobutyl, 1-ethylpropyl)) optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy, propoxy) optionally substituted by 1 to 3 $C_{1-6}$ alkoxy groups (e.g., methoxy),

(b) $C_{6-14}$ aryloxy group (e.g., phenyloxy),

(c) $C_{7-13}$ aralkyloxy group (e.g., benzyloxy),

(d) amino group optionally mono- or di-substituted by $C_{1-6}$ alkyl

group (e.g., methyl),

(e) 4- to 12-membered nonaromatic heterocyclic group (e.g., piperidyl, morphonyl),

(f) $C_{1-6}$ alkylsulfonyl group (e.g., methylsulfonyl, isopropylsulfonyl), and

(g) $C_{6-14}$ arylsulfonyl group (e.g., benzenesulfonyl),

(2) $C_{3-10}$ cycloalkyl group (e.g., cyclopentyl, cyclohexyl), or

(3) 5- or 6-membered heterocyclic group (e.g., pyridyl, piperidyl, tetrahydrothiopyranyl, 1-oxidotetrahydrothiopyranyl, 1,1-dioxidotetrahydrothiopyranyl) optionally substituted by 1 to 3 $C_{6-14}$ aryl groups (e.g., phenyl);

$R^{A4}$ is a hydrogen atom; and

$R^{A5}$ is $-(CH_2)_3-COOR^{A11}$ or $-NR^{A6}-(CH_2)_2-COOR^{A11}$, preferably $-NR^{A6}-(CH_2)_2-COOR^{A11}$

wherein $R^{A6}$ is a hydrogen atom or methyl (preferably, a hydrogen atom), and $R^{A11}$ is a hydrogen atom, methyl or ethyl (preferably, a hydrogen atom));

or a salt thereof.

[0126]

(compound AA-3)

A compound of the formula (IA), which is a compound of the formula (IA'), wherein

ring AA is a benzene ring or 6-membered aromatic heterocycle (e.g., pyridine);

ring AB is a 5-membered aromatic heterocycle (e.g., pyrrole, thiophene, furan, imidazole, pyrazole, pyrrole) optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 $C_{1-6}$ alkoxy groups (e.g., methoxy),

(b) $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl),

(c) $C_{6-14}$ aryl group (e.g., phenyl) optionally having 1 to 3 $C_{1-6}$ alkyl groups (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine),

(d) cyano group,

(e) $C_{1-6}$ alkoxy group (e.g., methoxy), and

(f) halogen atom (e.g., bromine atom);

ring AC is

(1) benzene ring optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine),

(b) $C_{3-10}$ cycloalkyl group (e.g., cyclopropyl, cyclohexyl),

(c) $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy, propoxy, isobutoxy) optionally substituted by 1 to 3 substituents selected from

(i) $C_{1-6}$ alkoxy group (e.g., methoxy),

(ii) $C_{3-6}$ cycloalkyl group (e.g., cyclopropyl),

(iii) 4- to 12-membered aromatic heterocyclic group (e.g., oxazolyl, isoxazolyl, pyridyl) optionally substituted by 1 to 3 substituents selected from

(i') halogen atom (e.g., fluorine, chlorine), and

(ii') $C_{1-6}$ alkyl group (e.g., methyl),

(iv) 4- to 12-membered nonaromatic heterocyclic group (e.g., oxetanyl, tetrahydrofuryl) optionally substituted by 1 to 3 $C_{1-6}$ alkyl groups (e.g., methyl),

(v) $C_{1-6}$ alkylsulfonyl group (e.g., methylsulfonyl),

(vi) $C_{1-6}$ alkylthio group (e.g., methylthio), and

(vii) hydroxy group,

(d) halogen atom (e.g., fluorine, chlorine),

(e) $C_{7-13}$ aralkyloxy group (e.g., benzyloxy),

(f) 4- to 12-membered non-aromatic heterocyclyl-oxy group (e.g., tetrahydropyranyloxy, tetrahydrothiopyranyloxy, 1,1-dioxidotetrahydrothiopyranyloxy),

(g) 4- to 12-membered aromatic heterocyclyl-oxy group (e.g., pyridyloxy) optionally substituted by 1 to 3 substituents selected from

(i) $C_{1-6}$ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine), and

(ii) cyano group,

(h) $C_{6-14}$ aryl group (e.g., phenyl),

(i) 4- to 12-membered aromatic heterocyclic group (e.g., oxazolyl, isoxazolyl, pyrazolyl, pyridyl) optionally substituted by 1 to 3 substituents selected from

(i) $C_{1-6}$ alkyl group (e.g., methyl), and

(ii) $C_{1-6}$ alkoxy group (e.g., methoxy),

(j) 4- to 12-membered nonaromatic heterocyclic group (e.g., morpholino, thiomorpholino),

(k) $C_{7-13}$ aralkyl group (e.g., benzyl),

(l) cyano group,

(m) amino group optionally mono- or di-substituted by substituent(s) selected from

(i) $C_{1-6}$ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 $C_{1-6}$ alkoxy groups (e.g., methoxy),

(ii) $C_{1-6}$ alkyl-carbonyl group (e.g., acetyl),

(iii) $C_{1-6}$ alkylsulfonyl group (e.g., methylsulfonyl),

(iv) carbamoyl group optionally mono- or di-substituted by $C_{1-6}$ alkyl group (e.g., ethyl),

(v) $C_{6-14}$ aryl-carbonyl group (e.g., benzoyl),

(vi) $C_{6-14}$ arylsulfonyl group (e.g., benzenesulfonyl), and

(vii) $C_{7-13}$ aralkyl group (e.g., benzyl), and

(n) $C_{6-14}$ arylsulfonyl group (e.g., benzenesulfonyl), or

(2) 5- or 6-membered aromatic heterocycle (e.g., pyridine) optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine),

(b) $C_{3-10}$ cycloalkyl group (e.g., cyclohexyl),

(c) $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 substituents selected from

(i) $C_{1-6}$ alkoxy group (e.g., methoxy), and

(ii) $C_{3-6}$ cycloalkyl group (e.g., cyclopropyl),

(d) halogen atom (e.g., fluorine, chlorine, bromine),

(e) $C_{7-13}$ aralkyloxy group (e.g., benzyloxy), and

(f) 4- to 12-membered non-aromatic heterocyclyl-oxy group

(e.g., tetrahydropyranyloxy);

$R^{A3}$ is

(1) $C_{1-6}$ alkyl group (preferably, methyl, ethyl, butyl, hexyl, branched $C_{1-6}$ alkyl group (e.g., isopropyl, isobutyl, 1-ethylpropyl)) optionally substituted by 1 to 3 substituents selected from

(a) $C_{1-6}$ alkoxy group (e.g., methoxy, ethoxy, propoxy) optionally substituted by 1 to 3 $C_{1-6}$ alkoxy groups (e.g., methoxy),

(b) $C_{6-14}$ aryloxy group (e.g., phenyloxy),

(c) $C_{7-13}$ aralkyloxy group (e.g., benzyloxy),

(d) amino group optionally mono- or di-substituted by $C_{1-6}$ alkyl group (e.g., methyl),

(e) 4- to 12-membered nonaromatic heterocyclic group (e.g., piperidyl, morphonyl),

(f) $C_{1-6}$ alkylsulfonyl group (e.g., methylsulfonyl, isopropylsulfonyl),

(g) $C_{6-14}$ arylsulfonyl group (e.g., benzenesulfonyl), and

(h) $C_{1-6}$ alkylthio group (e.g., methylthio),

(2) $C_{3-10}$ cycloalkyl group (e.g., cyclopentyl, cyclohexyl),

(3) 5- or 6-membered heterocyclic group (e.g., pyridyl, piperidyl, tetrahydrothiopyranyl, 1-oxidotetrahydrothiopyranyl, 1,1-dioxidotetrahydrothiopyranyl) optionally substituted by 1 to 3 $C_{6-14}$ aryl groups (e.g., phenyl), or

(4) $C_{6-14}$ aryl (e.g., phenyl);

$R^{A4}$ is a hydrogen atom; and

$R^{A5}$ is $-(CH_2)_3-COOR^{A11}$ or $-NR^{A6}-(CH_2)_2-COOR^{A11}$, preferably, $-NR^{A6}-(CH_2)_2-COOR^{A11}$

wherein $R^{A6}$ is a hydrogen atom or methyl (preferably, a hydrogen atom), and $R^{A11}$ is a hydrogen atom, methyl or ethyl (preferably, a hydrogen atom);

or a salt thereof.

[0127]

(compound AA-4)

3-{[(4-{[Cyclohexyl(3-methyl-1-benzofuran-2-

yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid or a salt thereof (Example A41);
3-{[(6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-yl)carbonyl](methyl)amino}propanoic acid or a salt thereof (Example A53);
3-{[(4-{[2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid or a salt thereof (Example A73);
3-[{[4-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid or a salt thereof (Example A78); or
3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid or a salt thereof (Example A83).

[0128]

As the salts of compounds (I) and (IA), pharmacologically acceptable salts are preferable. Examples of such salt include a salt with inorganic base, a salt with organic base, a salt with inorganic acid, a salt with organic acid, a salt with basic or acidic amino acid and the like.

[0129]

Preferable examples of a salt with inorganic base include alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt and the like; aluminum salt; ammonium salt and the like.

[0130]

Preferable examples of the salt with organic base include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, tromethamine [tris(hydroxymethyl)methylamine], tert-butylamine, cyclohexylamine, benzylamine, dicyclohexylamine, N,N-dibenzylethylenediamine and the like.

[0131]

Preferable examples of the salt with inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like.

[0132]

Preferable examples of the salt with organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

[0133]

Preferable examples of the salt with basic amino acid include salts with arginine, lysine, ornithine and the like.

[0134]

Preferable examples of the salt with acidic amino acid include salts with aspartic acid, glutamic acid and the like.

[0135]

The prodrug of compound (I) or (IA) means a compound which is converted to compound (I) or (IA) under the physiological condition in the living body by a reaction with an enzyme, a gastric acid, or the like, that is, by enzymatic oxidation, reduction, hydrolysis, etc.; by hydrolysis with gastric acid, etc.

[0136]

Examples of the prodrug of compound (I) and compound (IA) include a compound obtained by subjecting an amino group in compound (I) and compound (IA) to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino group in compound (I) and compound (IA) to an eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation); a compound obtained by subjecting a hydroxy group in compound (I) and

compound (IA) to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting a hydroxy group in compound (I) and compound (IA) to an acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation); a compound obtained by subjecting a carboxyl group in compound (I) and compound (IA) to an esterification or amidation (e.g., a compound obtained by subjecting a carboxyl group in compound (I) and compound (IA) to an ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification or methyl amidation etc.) and the like. These compounds can be produced from compound (I) and compound (IA) according to a method known *per se*.

[0137]

A prodrug for compound (I) and compound (IA) may also be one which is converted to compound (I) and compound (IA) under a physiological condition, such as those described in IYAKUHIN no KAIHATSU, Development of Pharmaceuticals, Vol. 7, Design of Molecules, p. 163-198, Published by HIROKAWA SHOTEN, 1990.

Compounds (I) and (IA) and prodrugs thereof (these are sometimes to be collectively abbreviated as "the compound of the present invention" in the present specification) include stereoisomers such as cis, trans isomer and the like, optically active forms such as racemate, R compound and S compound and the like. Depending on the kind of ring such as ring A and the like, isomers may be produced by conformation, and such isomers are also included in the compound of the present invention.

[0138]

The compound of the present invention may be labeled with

an isotope (e.g., $^{2}H$, $^{3}H$, $^{14}C$, $^{35}S$, $^{125}I$) and the like. The compound of the present invention may be hydrate, non-hydrate, solvate or non-solvate.

[0139]

The compound of the present invention has low toxicity, and can be used as an agent for the prophylaxis or treatment of various diseases mentioned below in a mammal (e.g., human, mouse, rat, rabbit, dog, cat, bovine, horse, swine, monkey) directly or in the form of a pharmaceutical composition by admixing with a pharmacologically acceptable carrier and the like.

[0140]

Here, examples of the pharmacologically acceptable carrier include various organic or inorganic carrier substances conventionally used as preparation materials, which are added as excipient, lubricant, binder or disintegrant for solid dosage forms; as solvent, solubilizing agent, suspending agent, isotonicity agent, buffer or soothing agent for liquid preparation, and the like. Where necessary, preparation additives such as preservative, antioxidant, colorant, sweetener and the like can also be used.

[0141]

Preferable examples of the excipient include lactose, sucrose, D-mannitol, D-sorbitol, starch, pregelatinized starch, dextrin, crystalline cellulose, low-substituted hydroxypropylcellulose, sodium carboxymethylcellulose, gum arabic, pullulan, light anhydrous silicic acid, synthetic aluminum silicate and magnesium aluminometasilicate.

[0142]

Preferable examples of the lubricant include magnesium stearate, calcium stearate, talc and colloidal silica.

[0143]

Preferable examples of the binder include pregelatinized starch, sucrose, gelatin, gum arabic, methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose,

crystalline cellulose, sucrose, D-mannitol, trehalose, dextrin, pullulan, hydroxypropylcellulose, hydroxypropylmethylcellulose and polyvinylpyrrolidone.

[0144]

Preferable examples of the disintegrant include lactose, sucrose, starch, carboxymethylcellulose, calcium carboxymethylcellulose, sodium croscarmellose, sodium carboxymethylstarch, light anhydrous silicic acid and low-substituted hydroxypropylcellulose.

[0145]

Preferable examples of the solvent include water for injection, physiological brine, Ringer's solution, alcohol, propylene glycol, polyethylene glycol, sesame oil, corn oil, olive oil and cottonseed oil.

[0146]

Preferable examples of the solubilizing agent include polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate and sodium acetate.

[0147]

Preferable examples of the suspending agent include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, lauryl aminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glyceryl monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like; polysorbates and polyoxyethylene hydrogenated castor oil.

[0148]

Preferable examples of the isotonicity agent include sodium chloride, glycerol, D-mannitol, D-sorbitol and glucose.

[0149]

Preferable examples of the buffer include buffers such as phosphate, acetate, carbonate, citrate and the like.

Preferable examples of the soothing agent include benzyl alcohol.

[0150]

Preferable examples of the preservative include paraoxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Preferable examples of the antioxidant include sulfite, ascorbate and the like.

[0151]

Preferable examples of the colorant include aqueous food tar colors (e.g., food colors such as Food Red No. 2 and No. 3, Food Yellow No. 4 and No. 5, Food Blue No. 1 and No. 2, etc.), water insoluble lake dye (e.g., aluminum salt of the above-mentioned aqueous food tar color) and natural dye (e.g., β-carotene, chlorophyll, red iron oxide).

[0152]

Preferable examples of the sweetening agent include sodium saccharin, dipotassium glycyrrhizinate, aspartame and stevia.

[0153]

Examples of the dosage form of the above-mentioned pharmaceutical composition include oral preparations such as tablets (inclusive of sugar-coated tablets, film-coated tablets, sublingual tablets, orally disintegrating tablets), capsules (inclusive of soft capsules, microcapsules), granules, powders, troches, syrups, emulsions, suspensions, films (e.g., orally disintegrable films) and the like; and parenteral agents such as injections (e.g., subcutaneous injections, intravenous injections, intramuscular injections, intraperitoneal injections, drip infusions), external preparations (e.g., dermal preparations, ointments), suppository (e.g., rectal suppositories, vaginal suppositories), pellets, nasal preparations, pulmonary

preparations (inhalants), eye drops and the like. These may be safely administered orally or parenterally (e.g., topically, rectally, intravenously administered).

[0154]

These preparations may be release control preparations (e.g., sustained-release microcapsule) such as immediate-release preparation, sustained-release preparation and the like.

[0155]

A pharmaceutical composition can be produced by a method conventionally used in the technical field of pharmaceutical preparation, for example, the method described in the Japanese Pharmacopoeia and the like.

[0156]

While the content of the compound of the present invention in the pharmaceutical composition varies depending on the dosage form, dose of the compound of the present invention, and the like, it is, for example, about 0.1 to 100 wt%.

[0157]

During production of an oral preparation, coating may be applied as necessary for the purpose of masking of taste, enteric property or durability.

[0158]

Examples of the coating base to be used for coating include sugar coating base, aqueous film coating base, enteric film coating base and sustained-release film coating base.

[0159]

As the sugar coating base, sucrose is used. Moreover, one or more kinds selected from talc, precipitated calcium carbonate, gelatin, gum arabic, pullulan, carnauba wax and the like may be used in combination.

[0160]

Examples of the aqueous film coating base include cellulose polymers such as hydroxypropyl cellulose,

hydroxypropylmethyl cellulose, hydroxyethyl cellulose, methylhydroxyethyl cellulose etc.; synthetic polymers such as polyvinylacetal diethylaminoacetate, aminoalkyl methacrylate copolymer E [Eudragit E (trade name)], polyvinylpyrrolidone etc.; and polysaccharides such as pullulan etc.

[0161]

Examples of the enteric film coating base include cellulose polymers such as hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylethyl cellulose, cellulose acetate phthalate etc.; acrylic polymers such as methacrylic acid copolymer L [Eudragit L (trade name)], methacrylic acid copolymer LD [Eudragit L-30D55 (trade name)], methacrylic acid copolymer S [Eudragit S (trade name)] etc.; and naturally occurring substances such as shellac etc.

[0162]

Examples of the sustained-release film coating base include cellulose polymers such as ethyl cellulose etc.; and acrylic polymers such as aminoalkyl methacrylate copolymer RS [Eudragit RS (trade name)], ethyl acrylate-methyl methacrylate copolymer suspension [Eudragit NE (trade name)] etc.

[0163]

The above-mentioned coating bases may be used after mixing with two or more kinds thereof at appropriate ratios. For coating, for example, a light shielding agent such as titanium oxide, diiron trioxide and the like can be used.

[0164]

The compound of the present invention shows low toxicity (e.g., acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, cardiotoxicity, carcinogenicity and the like) and a few side effects. Therefore, it can be used as an agent for the prophylaxis or treatment or a diagnostic of various diseases in a mammal (e.g., human, bovine, horse, dog, cat, monkey, mouse, rat).

[0165]

The compound of the present invention has a superior glucagon antagonistic action.

The compound of the present invention can improve the state involving promoted function of glucagon (e.g., excess sugar production from the liver, excess secretion of growth hormone, excess suppression of gastric motility and the like) by, for example, shutting off the action of glucagon. Hence, the compound of the present invention can be useful as a glucagon antagonist, a sugar production-suppressive agent, a prophylactic or therapeutic agent for diseases involving promoted action of glucagon and the like.

[0166]

Specifically, the compound of the present invention can be used as a prophylactic or therapeutic agent for obesity, diabetes (e.g., type 1 diabetes, type 2 diabetes, gestational diabetes, obese diabetes), hyperlipidemia (e.g., hypertriglyceridemia, hypercholesterolemia, hypoHDL-emia, postprandial hyperlipemia), hypertension, cardiac failure, diabetic complications [e.g., neuropathy, nephropathy, retinopathy, diabetic cardiomyopathy, cataract, macroangiopathy, osteopenia, hyperosmolar diabetic coma, infections (e.g., respiratory infection, urinary tract infection, gastrointestinal infection, dermal soft tissue infections, inferior limb infection), diabetic gangrene, xerostomia hypacusis, hypacusis, cerebrovascular disorder, peripheral blood circulation disorder], metabolic syndrome (pathology containing three or more selected from hyper-triglycerid(TG)emia, hypo-HDL cholesterol (HDL-C)emia, hypertension, abdomen obesity and impaired glucose tolerance), sarcopenia and the like.

[0167]

For diagnostic criteria of diabetes, Japan Diabetes Society reported new diagnostic criteria in 1999.

[0168]

According to this report, diabetes is a condition showing any of a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 126 mg/dl, a 75 g oral glucose tolerance test (75 g OGTT) 2 hr level (glucose concentration of intravenous plasma) of not less than 200 mg/dl, and a non-fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 200 mg/dl. A condition not falling under the above-mentioned diabetes and different from "a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of less than 110 mg/dl or a 75 g oral glucose tolerance test (75 g OGTT) 2 hr level (glucose concentration of intravenous plasma) of less than 140 mg/dl" (normal type) is called a "borderline type".

[0169]

In addition, ADA (American Diabetes Association) in 1997 and WHO in 1998 reported new diagnostic criteria of diabetes.

[0170]

According to these reports, diabetes is a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 126 mg/dl and a 75 g oral glucose tolerance test 2 hr level (glucose concentration of intravenous plasma) of not less than 200 mg/dl.

[0171]

According to the above-mentioned reports, impaired glucose tolerance is a condition showing fasting blood glucose level (glucose concentration of intravenous plasma) of less than 126 mg/dl and a 75 g oral glucose tolerance test 2 hr level (glucose concentration of intravenous plasma) of not less than 140 mg/dl and less than 200 mg/dl. According to the report of ADA, a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 110 mg/dl and less than 126 mg/dl is called IFG (Impaired Fasting Glucose). According to the report of WHO, among the IFG (Impaired Fasting Glucose), a condition showing

a 75 g oral glucose tolerance test 2 hr level (glucose concentration of intravenous plasma) of less than 140 mg/dl is called IFG (Impaired Fasting Glycemia).

[0172]

The compound of the present invention can be also used as an agent for the prophylaxis or treatment of diabetes, borderline type, impaired glucose tolerance, IFG (Impaired Fasting Glucose) and IFG (Impaired Fasting Glycemia), as determined according to the above-mentioned new diagnostic criteria. Moreover, the compound of the present invention can prevent progress of borderline type, impaired glucose tolerance, IFG (Impaired Fasting Glucose) or IFG (Impaired Fasting Glycemia) into diabetes.

[0173]

Moreover, the compound of the present invention can also be used as a prophylactic or therapeutic agent for osteoporosis, cachexia (e.g., carcinocachexia, tuberculous cachexia, diabetic cachexia, hemopathic cachexia, endocrinopathic cachexia, infectious cachexia, cachexia in cardiac disease or cachexia induced by acquired immunodeficiency syndrome), fatty liver, polycystic ovary syndrome, renal diseases (e.g., diabetic nephropathy, glomerulonephritis, glomerulosclerosis, nephrosissyndrome, hypertensive nephrosclerosis, end-stage renal disorder), muscular dystrophy, myocardial infarction, angina pectoris, cerebrovascular disorder (e.g., cerebral infarction, cerebral apoplexy), ischemia, coronary heart disease, non-Q wave myocardial infarction (non-Q wave MI), congestive heart failure, ventricular hypertrophy, cardiac arrhythmia, intermittent claudication, peripheral obstructive arterial disease (e.g., peripheral arterial disorder), Alzheimer's disease, Parkinson's disease, anxiety, dementia, insulin resistance syndrome, syndrome X, hyperinsulinemia, perception disorder in hyperinsulinemia, tumor (e.g., leukemia, breast cancer, prostate cancer, skin cancer, epithelial cancer,

glandular cancer), irritable bowel syndrome, acute or chronic diarrhea, inflammatory disease (e.g., chronic rheumatoid arthritis, spondylitis deformans, osteoarthritis, lumbago, gout, gouty arthritis, inflammation after operation or trauma, swelling, neuralgia, pharyngolaryngitis, cystitis, hepatitis (including nonalcoholic steatohepatitis), pneumonia, pancreatitis, enteritis, inflammatory bowel disease (including inflammatory colitis), ulcerative colitis, gastric mucosa injury (including gastric mucosa injury caused by aspirin), Lyme disease, rubella arthritis, psoriatic arthritis, conjunctivitis, gastritis, chronic thyroiditis, chronic active hepatitis, Crohn's disease, synovitis, ankylosing spondylitis), small intestinal mucosa injury, malabsorption, testis dysfunction, visceral obesity syndrome, sarcopenia, macular degeneration, hypoplastic anemia, thrombocytopenia, multiple sclerosis, periodontal disease, keloid formation, lung sarcoidosis, myasthenia gravis, Reiter's syndrome, influenza, cerebral malaria, silicosis, bone resorption disease, fever, muscular pain, bone diseases related to multiple myeloma, neurodegenerative diseases due to trauma, traumatic brain injury, giantism, graft vs host reaction, transplant rejection, skin condition (e.g., scar tissue formation, eczema, atopic dermatitis, contact dermatitis, urticaria, scleroderma, psoriasis), allergy or respiratory diseases (e.g., asthma, respiratory distress syndrome, hay fever, allergic rhinitis, chronic lung inflammatory disease (e.g., chronic obliterative pulmonary diseases (COPD)), inflammation relating to autoimmune diseases (e.g., systemic lupus erythematosus, Addison's disease, polyglandular deficiency syndrome, Graves' disease, infectious disease (e.g., sepsis, septic shock, Shigellosis, helicobacter pylori), viral disease (e.g., simple herpes virus infection, cytomegalovirus infection, Epstein-Barr virus infection, human immunodeficiency virus infection, A-type, B-type and C-type hepatitis virus infection, angiogenetic disease (e.g., solid tumor, ocular

neovasculization, Hemangioma, edema, analgesia, pain (e.g., neuromuscular pain, headache, pain caused by cancer or operation, toothache, arthritic pain), irritable bowel syndrome, leukemia, central nervous system diseases (e.g., due to cerebral ischemia, cerebral infarction, brain edema and the like), renal fibrosis, hepatic fibrosis, prostate fibrosis, lung fibrosis and the like.

[0174]

Moreover, the compound of the present invention can also be used as a gastrointestinal motility function improver.

The compound of the present invention can also be used for secondary prevention and suppression of progression (e.g., secondary prevention and suppression of progression of cardiovascular events such as myocardial infarction and the like) of the above-mentioned various diseases.

[0175]

While the subject of administration of the compound of the present invention is not particularly limited, a mammal (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human and the like) is preferable.

While the dose of the compound of the present invention varies depending on the subject of administration, administration route, target disease, symptom and the like, for example, for oral administration to an adult diabetic patient, it is generally about 0.01 to 100 mg/kg body weight, preferably 0.05 to 30 mg/kg body weight, more preferably 0.1 to 10 mg/kg body weight for one dose, which is desirably administered once to 3 times a day.

[0176]

With the aim of enhancing the action of the compound of the present invention or decreasing the dose of the compound and the like, the compound can be used in combination with medicaments such as therapeutic agents for diabetes, therapeutic agents for diabetic complications, therapeutic agents for hyperlipidemia, antihypertensive agents,

antiobesity agents, diuretics, antithrombotic agents and the like (hereinafter to be abbreviated as concomitant drug). The time of administration of the compound of the present invention and that of the concomitant drug are not limited, and they may be administered simultaneously or in a staggered manner to the administration subject. In addition, the compound of the present invention and the concomitant drug may be administered as two kinds of preparations containing respective active ingredients or a single preparation containing both active ingredients.

[0177]

The dose of the concomitant drug can be appropriately determined based on the dose employed clinically. In addition, the mixing ratio of the compound of the present invention and the concomitant drug can be appropriately determined according to the administration subject, administration route, target disease, condition, combination, and the like. For example, when the administration subject is a human, the concomitant drug may be used in an amount of 0.01 to 100 parts by weight per 1 part by weight of the compound of the present invention.

[0178]

Examples of the therapeutic agent for diabetes include insulin preparations [e.g., animal insulin preparations extracted from the bovine or swine pancreas; human insulin preparations synthesized by a genetic engineering technique using Escherichia coli or a yeast; insulin zinc; protamine zinc insulin; a fragment or a derivative of insulin (e.g., INS-1, etc.)], oral insulin preparation), insulin sensitizer (e.g., pioglitazone or a salt thereof (preferably hydrochloride), TAK-379, rosiglitazone or a salt thereof (preferably maleate), tesaglitazar, Ragaglitazar, muraglitazar, edaglitazone, metaglidasen, Naveglitazar, AMG-131, THR-0921), α-glucosidase inhibitor (e.g., voglibose, acarbose, miglitol, emiglitate), biguanide (e.g., metformin, buformin or a salt thereof (e.g., hydrochloride, fumarate, succinate)), insulin

secretagogue [sulfonylurea (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride, glipizide, glybuzole), repaglinide, nateglinide, mitiglinide or calcium salt hydrate thereof, glucose dependency insulin secretagogue (e.g., TAK-875)], dipeptidyl peptidase IV inhibitor (e.g., alogliptin, Vildagliptin, sitagliptin, saxagliptin, T-6666, TS-021), β3 agonist (e.g., AJ-9677), GPR40 agonist, GLP-1 receptor agonist [e.g., GLP-1, GLP-1MR, NN-2211, AC-2993 (exendin-4), BIM-51077, Aib(8,35)hGLP-1(7,37)$NH_2$, CJC-1131], amylin agonist (e.g., pramlintide), phosphotyrosine phosphatase inhibitors (e.g., sodium vanadate), gluconeogenesis inhibitor (e.g., glycogen phosphorylase inhibitor, glucose-6-phosphatase inhibitors, glucagon antagonists), SGLUT (sodium-glucose cotransporter)inhibitor (e.g., T-1095), 11β-hydroxysteroid dehydrogenase inhibitor (e.g., BVT-3498), adiponectin or an agonist thereof, IKK inhibitor (e.g., AS-2868), leptin resistance improving drugs, somatostatin receptor agonists, glucokinase activators (e.g., Ro-28-1675), GIP(Glucose-dependent insulinotropic peptide) and the like.

[0179]

Examples of the therapeutic agents for diabetic complications include aldose reductase inhibitors (e.g., tolrestat, epalrestat, zenarestat, zopolrestat, minalrestat, fidarestat, CT-112), neurotrophic factor and an increasing drug thereof (e.g., NGF, NT-3, BDNF, neurotrophin production and secretion promoter described in WO01/14372 (e.g., 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-[3-(2-methylphenoxy)propyl]oxazole)), TAK-583, nerve regeneration promoter (e.g., Y-128), PKC inhibitor (e.g., ruboxistaurin mesylate), AGE inhibitor (e.g., ALT946, pimagedine, pyratoxanthine, N-phenacylthiazolium bromide (ALT766), ALT-711, EXO-226, Pyridorin, pyridoxamine), active oxygen scavengers (e.g., thioctic acid), cerebral vasodilator (e.g., tiapuride, mexiletine), somatostatin receptor agonists (e.g., BIM23190),

apoptosis signal regulating kinase-1 (ASK-1) inhibitor and the like.

[0180]

Examples of the therapeutic agent for hyperlipidemia include statin compound (e.g., pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, rosuvastatin, pitavastatin or a salt thereof (e.g., sodium salt, calcium salt)), squalene synthase inhibitors (e.g., lapaquistat acetate or a salt thereof), fibrate compound (e.g., bezafibrate, clofibrate, simfibrate, clinofibrate), ACAT inhibitor (e.g., Avasimibe, Eflucimibe), anion exchange resin (e.g., colestyramine), probucol, nicotinic acid drug (e.g., nicomol, niceritrol), ethyl icosapentate, phytosterol (e.g., soysterol, gamma oryzanol (γ-oryzanol)) and the like.

[0181]

Examples of the antihypertensive agent include angiotensin converting enzyme inhibitor (e.g., captopril, enalapril, delapril), angiotensin II antagonist (e.g., candesartan cilexetil, losartan, eprosartan, valsartan, telmisartan, irbesartan, tasosartan, 1-[[2'-(2,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-2-ethoxy-1H-benzimidazole-7-carboxylic acid, TAK-491), calcium antagonist (e.g., manidipine, nifedipine, amlodipine, efonidipine, nicardipine), potassium channel opener (e.g., levcromakalim, L-27152, AL 0671, NIP-121), clonidine and the like.

[0182]

Examples of the antiobesity agent include central-acting antiobesity agent (e.g., dexfenfluramine, fenfluramine, phentermine, sibutramine, amfepramone, dexamphetamine, mazindol, phenylpropanolamine, clobenzorex; MCH receptor antagonists (e.g., SB-568849; SNAP-7941; compounds described in WO01/82925 and WO01/87834); neuropeptide Y antagonist (e.g., CP-422935); cannabinoid receptor antagonists (e.g., SR-141716, SR-147778); ghrelin antagonist; 11β-hydroxysteroid dehydrogenase inhibitor (e.g., BVT-3498)), pancreatic lipase

inhibitors (e.g., orlistat, cetilistat), β3 agonist (e.g., AJ-9677, AZ40140), anorectic peptides (e.g., leptin, CNTF (ciliary neurotrophic factor)), cholecystokinin agonist (e.g., lintitript, FPL-15849), feeding deterrent (e.g., P-57) and the like.

[0183]

Examples of the diuretics include xanthine derivatives (e.g., theobromine sodium salicylate, theobromine calcium salicylate), thiazide preparations (e.g., ethiazide, cyclopenthiazide, trichloromethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, polythiazide, methyclothiazide), antialdosterone preparations (e.g., spironolactone, triamterene), carbonic anhydrase inhibitors (e.g., acetazolamide), chlorobenzenesulfonamide agents (e.g., chlortalidone, mefruside, indapamide), azosemide, isosorbide, ethacrynic acid, piretanide, bumetanide and furosemide and the like.

[0184]

Examples of the antithrombotic agent include heparin (e.g., heparin sodium, heparin calcium, dalteparin sodium (dalteparin sodium)), warfarin (e.g., warfarin potassium), anti-thrombin drug (e.g., aragatroban, dabigatran), thrombolytic agent (e.g., urokinase, tisokinase, alteplase, nateplase, monteplase, pamiteplase), platelet aggregation inhibitor (e.g., ticlopidine hydrochloride, cilostazol), ethyl icosapentate, beraprost sodium, sarpogrelate hydrochloride, E5555, SHC 530348, prasugrel), FXa inhibitor (e.g., TAK-442, rivaroxaban, apixaban, DU-176b, YM150) and the like can be mentioned.

[0185]

The above-mentioned concomitant drug may be a combination of two or more kinds at an appropriate ratio.

[0186]

The production methods of the compound of the present invention are explained in the following.

The compound of the present invention can be produced according to a method known per se, for example, the methods described in detail in the following, or a method analogous thereto.

In the following production methods, the starting material compounds may be in the form of salts, and examples of such salt include those similar to the salts of compound (I) and compound (IA).

The compound obtained in each step of the following formulas may be used for the next reaction directly in the form of the reaction mixture or a crude product, or can be isolated and purified by known separation and purification means, for example, concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like and used for the next reaction.

When the compounds of the following formulas are commercially available, such commercially available products may be directly used.

In each of the following reactions, when the starting material compound has an amino group, a carboxy group or a hydroxy group as a substituent, such group may be protected by a protecting group generally used in the peptide chemistry and the like. In this case, the protecting group is removed as necessary after the reaction to give the object compound.

Examples of the amino-protecting group include a formyl group, a $C_{1-6}$ alkyl-carbonyl group, a $C_{1-6}$ alkoxy-carbonyl group, a benzoyl group, a $C_{7-10}$ aralkyl-carbonyl group (e.g., benzylcarbonyl), a $C_{7-14}$ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl), a trityl group, a phthaloyl group, a N,N-dimethylaminomethylene group, a substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), a $C_{2-6}$ alkenyl group (e.g., 1-allyl) and the like. These groups are optionally substituted by 1 to 3

substituents selected from a halogen atom, a $C_{1-6}$ alkoxy group and a nitro group.

Examples of the carboxy-protecting group include a $C_{1-6}$ alkyl group, a $C_{7-11}$ aralkyl group (e.g., benzyl), a phenyl group, a trityl group, a substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), a $C_{2-6}$ alkenyl group (e.g., 1-allyl) and the like.

Examples of the hydroxy-protecting group include a $C_{1-6}$ alkyl group, a phenyl group, a trityl group, a $C_{7-10}$ aralkyl group (e.g., benzyl), a formyl group, a $C_{1-6}$ alkyl-carbonyl group, a benzoyl group, a $C_{7-10}$ aralkyl-carbonyl group (e.g., benzylcarbonyl), a 2-tetrahydropyranyl group, a 2-tetrahydrofuranyl group, a substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), a $C_{2-6}$ alkenyl group (e.g., 1-allyl) and the like. These groups are optionally substituted by 1 to 3 substituents selected from a halogen atom, a $C_{1-6}$ alkyl group, a $C_{1-6}$ alkoxy group and a nitro group.

The above-mentioned protecting group can be removed according to a method known per se, for example, the method described in Protective Groups in Organic Synthesis, John Wiley and Sons (1980) and the like. Specifically, a method using acid, base, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, trialkylsilyl halide (e.g., trimethylsilyliodide, trimethylsilyl bromide and the like) and the like, a reduction method and the like are used.

[0187]

In each of the following reactions, introduction of substituent and functional group conversion reaction may be further performed by applying a method known per se to the starting material, intermediate and/or resultant product.

Examples of the substituent conversion reaction include methods known per se, for example, conversion to carboxy by

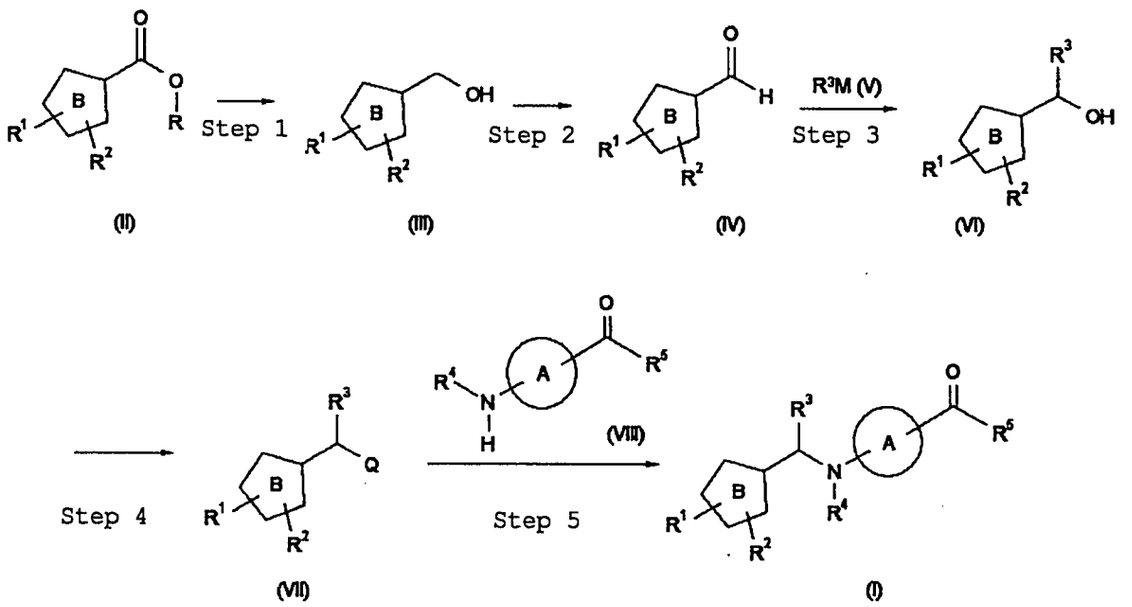
hydrolysis of ester, conversion to carbamoyl by amidation of carboxy, conversion to hydroxymethyl by reduction of carboxy, conversion to alcohol compound by reduction or alkylation of carbonyl, reductive amination of carbonyl, oximation of carbonyl, acylation, ureation, sulfonylation or alkylation of amino, substitution and amination of active halogen by amine, amination of nitro by reduction, alkylation of hydroxy, substitution and amination of hydroxy; alkylation of ring nitrogen atom of nitrogen-containing heterocycle, introduction of substituent by coupling reaction (e.g., aryl coupling reaction); substitution of halogen by amine, alcohol or thiol; and the like.

[0188]

Compound (I) can be produced, for example, by a method shown in the following Reaction scheme 1.

Reaction scheme 1

[0189]




[0190]

wherein R is a $C_{1-6}$ alkyl group (e.g., methyl, ethyl, n-hexyl); Q is a leaving group (e.g., methanesulfonyloxy group, p-toluenesulfonyloxy group, halogen atom (e.g., chlorine, bromine)); $R^3M$ is an organic metal compound (to be mentioned later), and other symbols are as defined above.

[0191]

step 1

Compound (III) can be produced by subjecting starting material compound (II) to a reduction reaction. This reduction reaction can be performed using a reducing agent and according to a conventional method.

Examples of the reducing agent include metal hydrogen compounds such as sodium bis(2-methoxyethoxy)aluminum hydride, diisobutylaluminum hydride (DIBALH) and the like; metal hydrogen complex compounds such as sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride, sodium aluminum hydride and the like and the like.

The amount of the reducing agent to be used is generally 1 - 20 mol per 1 mol of compound (II).

[0192]

This reaction is preferably performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, alcohols such as methanol, ethanol, propanol, isopropanol, butanol, isobutanol, tert-butanol and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, trichloroethylene and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, dimethoxyethane and the like; mineral acids such as hydrochloric acid, sulfuric acid and the like; organic acids such as formic acid, acetic acid, propionic acid, trifluoroacetic acid, methanesulfonic acid and the like; water; and the like can be mentioned. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

[0193]

The reaction time is generally 10 min - 48 hr, preferably 15 min - 24 hr.

The reaction temperature is generally -100°C to 150°C, preferably -20°C to 100°C.

[0194]

Compound (II) to be used as a starting material can be synthesized according to a method known per se, for example, the synthesis method described in WO2007/89031, EP94154, WO2003/99793 or EP1176140, or a method analogous thereto.

[0195]

step 2

compound (IV) can be produced by subjecting compound (III) to an oxidation reaction. The oxidation reaction can be performed using an oxidant and according to a conventional method.

Examples of the oxidant include active manganese dioxide, pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), Dess-Martin periodinane, dimethyl sulfoxide-acid anhydride (e.g., acetic anhydride, trifluoroacetic anhydride), dimethyl sulfoxide-thionyl chloride, dimethyl sulfoxide-sulfuryl chloride, dimethyl sulfoxide-oxalyl chloride, dimethyl sulfoxide-chlorine, and dimethylsulfoxide-dicyclohexylcarbodiimide (DCC) in the presence of acid (e.g., phosphoric acid, trifluoroacetic acid, dichloroacetic acid) and the like.

The amount of the oxidant to be used is generally 1 - 20 mol per 1 mol of compound (III).

[0196]

This reaction is preferably performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, ethers such as diethyl ether, diisopropyl ether, diphenylether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; ketones such as acetone, methylethyl ketone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, trichloroethylene and the like; aromatic hydrocarbons such as benzene, toluene and the

like; saturated hydrocarbons such as cyclohexane, hexane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoramide and the like; mineral acids such as hydrochloric acid, sulfuric acid and the like; organic acids such as formic acid, acetic acid, propionic acid, trifluoroacetic acid, methanesulfonic acid and the like; water; and the like. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

[0197]

The reaction time is generally 10 min - 48 hr, preferably 15 min - 24 hr.

The reaction temperature is generally -100°C to 150°C, preferably -20°C to 100°C.

[0198]

step 3

Compound (VI) can be produced by reacting compound (IV) with organic metal compound (V).

This reaction is performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane and the like; aliphatic hydrocarbons such as hexane, heptane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; and the like. These solvents may be used in a mixture at an appropriate ratio.

[0199]

Examples of the organic metal compound (V) include Grignard reagent (e.g., a compound represented by formula: $R^3MgBr$), organic lithium reagent (e.g., a compound represented by formula: $R^3Li$), organic zinc reagent (e.g., a compound represented by formula: $(R^3)_2Zn$), wherein $R^3$ is as defined above) and the like. Such compound can be produced according to a method known per se, for example, the method described in "Jikken Kagaku Kouza (The Chemical Society of Japan ed.), 4th Edition, vol. 25, Synthesis by Organic Metal Reagent" pp. 9-449,

Maruzen Press 1992, or a method analogous thereto.

The amount of the organic metal compound (V) to be used is generally about 1 - 10 mol, preferably about 1 - 2 mol, per 1 mol of compound (IV).

[0200]

The reaction temperature is generally -80°C to 100°C, preferably -20°C to 50°C.

The reaction time is generally 0.5 - 20 hr.

[0201]

step 4

compound (VII) can be produced by converting the hydroxy group of compound (VI) to a leaving group.

Such conversion to a leaving group can be performed according to a conventional method, for example, by reacting with methanesulfonyl chloride in the presence of an appropriate base, or by reacting with thionyl chloride.

Examples of the base to be used for this reaction include N,N-diisopropylethylamine (DIEA), triethylamine (TEA), pyridine, N,N-dimethylaniline and the like.

The amount of the methanesulfonyl chloride or thionyl chloride to be used is generally about 1 - 50 mol, preferably about 1 - 10 mol, per 1 mol of compound (VI).

The amount of the base to be used is generally about 1 - 50 mol, preferably about 1 - 10 mol, per 1 mol of compound (VI).

[0202]

This reaction is performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; and the like. These solvents may be used in a mixture at an appropriate ratio.

[0203]

The reaction temperature is generally -50 - 150°C, preferably -10 - 100°C.

The reaction time is generally 0.5 - 20 hr.

[0204]

step 5

Compound (I) can be produced by reacting compound (VII) with compound (VIII) (e.g., ethyl 3-{((4-aminophenyl)carbonyl)amino}propanoate) in the presence of a base. Where necessary, the ester group of the obtained adduct may be hydrolyzed.

[0205]

Examples of the base to be used for this reaction include alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkaline earth metal hydroxides such as magnesium hydroxide, calcium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; alkali metal hydrogencarbonates such as sodium hydrogen carbonate, potassium hydrogen carbonate and the like; alkali metal alkoxides having 1 to 6 carbon atoms such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; metal hydrides such as sodium hydride, potassium hydride, calcium hydride and the like and the like.

[0206]

This reaction is preferably performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, alcohols such as methanol, ethanol, 1-propanol, 2-propanol, tert-butyl alcohol and the like; ethers such as 1,4-dioxane, tetrahydrofuran, diethyl ether, dimethoxyethane, tert-butyl methyl ether, diisopropyl ether, ethylene glycol dimethylether and the like; esters such as ethyl formate, ethyl acetate, n-butyl acetate and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, trichloroethylene and the like; hydrocarbons such as n-hexane, benzene, toluene and the like;

amides such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide and the like; nitriles such as acetonitrile, propionitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; sulfolane; hexamethylphosphoramide; and the like. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

[0207]

In this reaction, 1 equivalent amount to a large excess amount (preferably 1 - 10 equivalents) of alkali metal iodide such as sodium iodide and the like may be added as a reaction promoter to compound (VII).

[0208]

The amount of the compound (VIII) to be used is generally about 1 - 10 mol, preferably about 1 - 2 mol, per 1 mol of compound (VII).

The amount of the base to be used is generally 1 - 10 molar equivalents, preferably 1 - 5 molar equivalents, per 1 mol of compound (VII).

[0209]

The reaction temperature is generally -30 - 200°C, preferably 0 - 150°C.

The reaction time is generally 0.5 - 20 hr.

The ester group can be hydrolyzed according to a method known per se, for example, the method described in Protective Groups in Organic Synthesis, Third Edition, Wiley-Interscience (1999) or a method analogous thereto.

[0210]

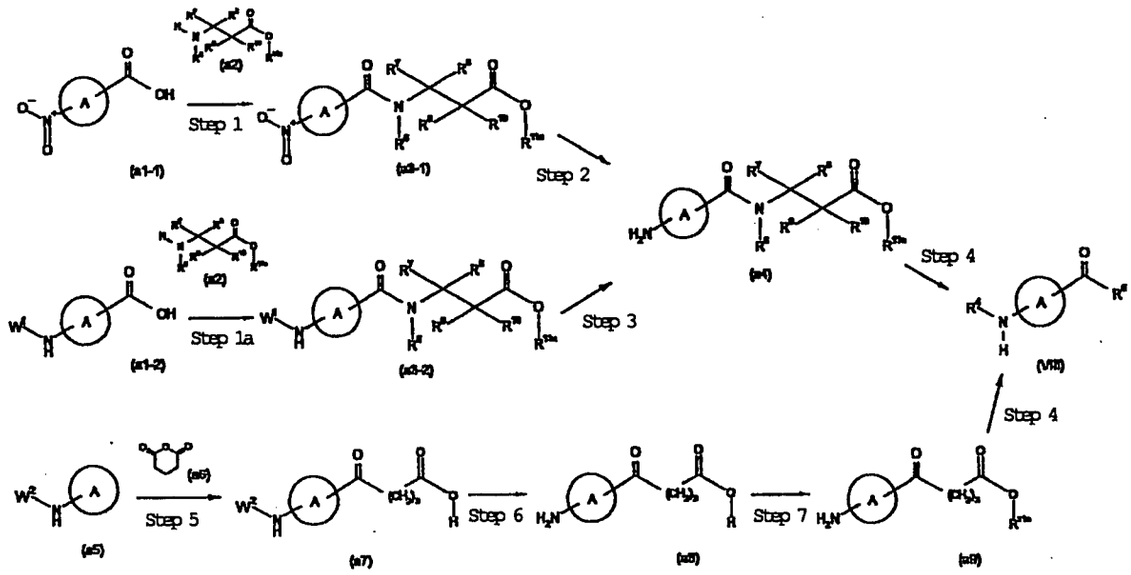
The production methods of the starting material compounds and reactive derivatives thereof to be used for the above-mentioned methods are explained in the following.

[0211]

Compound (VIII) can be produced according to, for example, the following Reaction scheme 2.

Reaction scheme 2

[0212]




[0213]

wherein $W^1$ and $W^2$ are each independently an amino-protecting group, $R^{11a}$ is a $C_{1-6}$ alkyl group, and other symbols are as defined above.

[0214]

step 1

In this reaction, compound (a1-1) is condensed with compound (a2) to give compound (a3-1).

The condensation reaction can be performed according to a conventional method, for example, a general peptide coupling method. Examples of the method include a method including direct condensation of compound (a1-1) and compound (a2) using a condensation agent, a method including reaction of a reactive derivative of compound (a1-1) with compound (a2) and the like.

Examples of the condensation agent include carbodiimide condensation reagents such as dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIPC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), hydrochloride thereof and the like; phosphoric acid condensation reagents such as diethyl cyanophosphate, diphenylphosphoryl azide and the like; carbonyldiimidazole, 2-chloro-1,3-dimethylimidazolium tetrafluoroborate, 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-

tetramethyluronium hexafluorophosphate (HATU) and the like.

[0215]

Examples of the solvent to be used for the condensation reaction include amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethyl sulfoxide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile, propionitrile and the like; water; and the like. These solvents may be used in a mixture at an appropriate ratio.

[0216]

The amount of the compound (a2) to be used is generally 1 - 10 mol, preferably 1 - 3 mol, per 1 mol of compound (a1-1).

[0217]

The amount of the condensation agent to be used is generally 0.1 - 10 mol, preferably 0.3 - 3 mol, per 1 mol of compound (a1-1).

[0218]

When a carbodiimide condensation reagent is used as the condensation agent, the reaction efficiency can be improved by using a suitable condensation promoter (e.g., 1-hydroxy-7-azabenzotriazole, 1-hydroxybenzotriazole, N-hydroxysuccinimide, N-hydroxyphthalimide) as necessary.

When HATU or phosphoric acid condensation reagent is used as the condensation agent, the reaction efficiency can be improved by using an organic amine base such as triethylamine, N,N-diisopropylethylamine and the like.

The amount of the condensation promoter or organic amine base to be used is generally 0.1 - 10 mol, preferably 0.3 - 3 mol, per 1 mol of compound (a1-1), respectively.

[0219]

The reaction temperature is generally -30 - 120°C, preferably -10 - 100°C.

The reaction time is generally 0.5 - 60 hr.

[0220]

Examples of the reactive derivative of compound (a1-1) include acid halide (e.g., acid chloride, acid bromide), imidazolide, mixed acid anhydride (e.g., anhydride with methyl carbonate, ethyl carbonate or isobutyl carbonate) and the like.

[0221]

For example, when an acid halide is used, the reaction is generally performed in the presence of a base, and in a solvent that does not adversely influence the reaction.

Examples of the base include amines such as triethylamine, pyridine, N-methylmorpholine, N,N-dimethylaniline, 4-dimethylaminopyridine and the like; alkali metal salt such as lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium hydrogen carbonate, sodium carbonate, potassium carbonate and the like; and the like.

[0222]

Examples of the solvent that does not adversely influence the reaction include amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethyl sulfoxide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile, propionitrile and the like; water; and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

When the above-mentioned amide is used as the solvent, the reaction can also be performed in the absence of a base.

[0223]

The amount of the compound (a2) to be used is generally 1

- 10 mol, preferably 1 - 5 mol, per 1 mol of acid halide of compound (a1-1).

[0224]

The amount of the base to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of acid halide of compound (a1-1).

[0225]

The reaction temperature is generally -30°C - 120°C, preferably -10 - 100°C.

The reaction time is generally 0.5 - 30 hr.

[0226]

When mixed acid anhydride is used, compound (a1-1) is reacted with chlorocarbonate (e.g., methyl chlorocarbonate, ethyl chlorocarbonate, isobutyl chlorocarbonate) in the presence of a base and then reacted with compound (a2).

Examples of the base to be used for this reaction include the aforementioned, those exemplified as the base to be used for the reaction of a acid halide of compound (a1-1) with compound (a2) and the like.

[0227]

The amount of the compound (a2) to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (a1-1).

The amount of the chlorocarbonate to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (a1-1).

The amount of the base to be used is generally 1 - 10 mol, preferably 1 - 3 mol, per 1 mol of compound (a1-1).

The reaction temperature is generally -30°C - 120°C, preferably -10 - 100°C.

The reaction time is generally 0.5 - 20 hr.

[0228]

When imidazolide is used, compound (a1-1) is reacted with, for example, N,N'-carbonyldiimidazole (CDI) to give the corresponding imidazolide, which is further reacted with compound (a2).

The amount of the compound (a2) to be used is generally 1

- 10 mol, preferably 1 - 5 mol, per 1 mol of compound (a1-1).

The amount of N,N'-carbonyldiimidazole (CDI) to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (a1-1).

The reaction temperature is generally -30°C - 120°C, preferably -10 - 100°C.

The reaction time is generally 0.5 - 20 hr.

[0229]

As compound (a1-1) and compound (a2), commercially available products are available, or can be produced using a commercially available compound according to a method known per se or a method analogous thereto.

[0230]

step 1a

Compound (a3-2) can be produced in the same manner as in step 1 and using compound (a1-2) and compound (a2).

As compound (a1-2), a commercially available product can be used, or can be produced using a commercially available compound according to a method known per se or a method analogous thereto.

[0231]

step 2

Compound (a4) can be produced by subjecting compound (a3-1) to a reduction reaction in the presence of a metal catalyst and a hydrogen source. Such reduction reaction can be performed according to a conventional method in a solvent that does not adversely influence the reaction.

[0232]

Examples of the metal catalyst to be used for this reaction include palladium-carbon, palladium black, palladium chloride, platinum oxide, platinum black, platinum-palladium, Raney-nickel, Raney cobalt and the like.

[0233]

Examples of the hydrogen source include hydrogen gas, formic acid, formic acid amine salt, phosphinate salt,

hydrazine and the like.

Examples of the solvent that does not adversely influence the reaction include methanol, tetrahydrofuran, N,N-dimethylacetamide and the like.

[0234]

The amount of the metal catalyst to be used is generally 0.001 - 1000 mol, preferably 0.01 - 100 mol, per 1 mol of compound (a3-1).

[0235]

The reaction temperature is generally -70 - 150°C, preferably -20 - 100°C.

The reaction time is generally 0.1 - 100 hr, preferably 0.1 - 40 hr.

[0236]

This reaction can also be performed in the presence of a reducing agent in a solvent that does not adversely influence the reaction.

Examples of the reducing agent include ferric oxide, zinc, tin and the like, and compound (a4) can be produced by the reaction described in "Jikken Kagaku Kouza (The Chemical Society of Japan ed.), 4th Edition, vol. 20, Organic Synthesis II Alcohol and Amine" pp. 279-280, Maruzen Press 1992, or a method analogous thereto.

[0237]

step 3

Compound (a4) can be produced by removing the protecting group ($W^1$) of compound (a3-2) by a method known per se, for example, the method described in Protective Groups in Organic Synthesis, Third Edition, Wiley-Interscience (1999) or a method analogous thereto.

[0238]

step 4

Compound (VIII) can be produced by subjecting compound (a4) or compound (a9) to a reductive amination reaction.

The reductive amination reaction can be performed by a

method known per se, for example, the method described in "Jikken Kagaku Kouza (The Chemical Society of Japan ed.), 4th Edition, vol. 20. Organic Synthesis II Alcohol and Amine" pp. 300-302, Maruzen Press 1992; the method described in Reductions in Organic Chemistry Second Edition, American Chemical Society (1996), pp. 187-189; or a method analogous thereto.

[0239]

step 5

Compound (a7) can be synthesized by Friedel-Crafts reaction using compound (a5) and glutaric anhydride (a6) and by the synthesis method described in, for example, WO2004/45616, or a method analogous thereto.

[0240]

step 6

Compound (a8) can be produced by removing the protecting group of compound (a7) by a method known per se, for example, the method described in Protective Groups in Organic Synthesis, Third Edition, Wiley-Interscience (1999) or a method analogous thereto.

[0241]

step 7

Compound (a9) can be produced by esterification of compound (a8) by a method known per se, for example, the method described in Protective Groups in Organic Synthesis, Third Edition, Wiley-Interscience (1999) or a method analogous thereto.

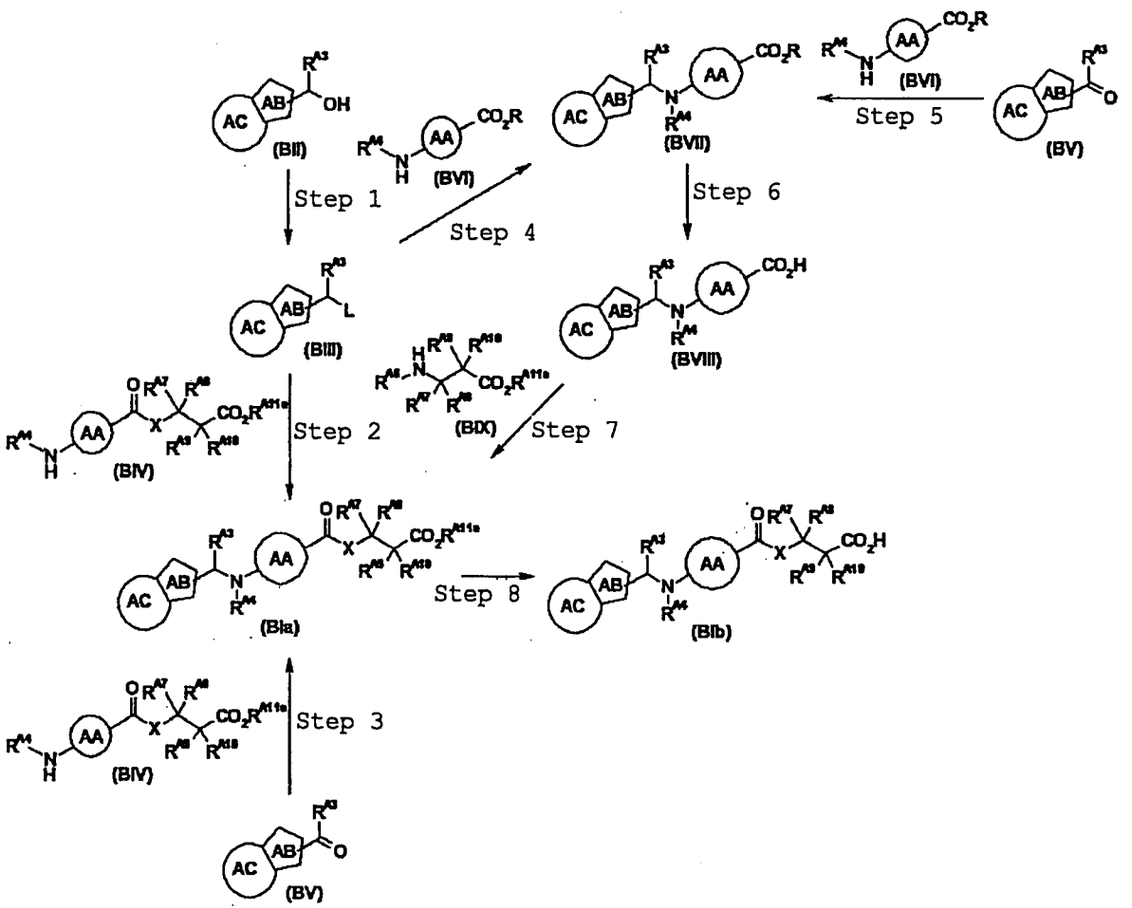
[0242]

Compound (IA) can be produced, for example, by the method shown in the following Reaction scheme A1.

In the following Reaction scheme A1, compound (BIa) includes a compound (IA) wherein $R^{A11}$ is $C_{1-6}$ alkyl group, and compound (BIb) includes a compound (IA) wherein $R^{A11}$ is a hydrogen atom.

Reaction scheme A1

[0243]




[0244]

wherein X is $CH_2$ or $NR^{A6}$, $R^{A11a}$ is a $C_{1-6}$ alkyl group, L is a leaving group (e.g., methanesulfonyloxy group, p-toluenesulfonyloxy group, halogen atom (e.g., chlorine, bromine)), and other symbols are each as defined above.

[0245]

step 1

Compound (BIII) can be produced, for example, by converting the hydroxy group of compound (BII) to a leaving group. Such conversion to a leaving group can be performed according to a conventional method, for example, reaction with methanesulfonylchloride, phosphoryl chloride or thionyl chloride in the presence of an appropriate base.

Examples of the base include N,N-diisopropylethylamine (DIEA), triethylamine (TEA), pyridine, N,N-dimethylaniline and the like.

The amount of the base to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (BII).

The amount of the methanesulfonylchloride, phosphoryl chloride or thionyl chloride to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (BII).

This reaction can be performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -80 - 200°C, preferably -10 - 150°C.

The reaction time is generally 10 min - 20 hr, preferably 15 min - 24 hr.

compound (BII) can be produced by the below-mentioned reaction.

[0246]

step 2

Compound (BIa) can be produced, for example, by reacting compound (BIII) with compound (BIV) in the presence of a base.

Examples of the base include alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkaline earth metal hydroxides such as magnesium hydroxide, calcium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; alkali metal hydrogencarbonates such as sodium hydrogen carbonate, potassium hydrogen carbonate and the like; alkali metal alkoxides having 1 to 6 carbon atoms such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; metal hydrides such as sodium hydride, potassium hydride, calcium hydride and the like; and the like.

The amount of the base to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (BIII).

This reaction is preferably performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, alcohols such as methanol, ethanol, 1-propanol, 2-propanol, tert-butyl alcohol and the like; ethers such as 1,4-dioxane, tetrahydrofuran, diethyl ether, dimethoxyethane, tert-butyl methyl ether, diisopropyl ether, ethylene glycol dimethylether and the like; esters such as ethyl formate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, trichloroethylene and the like; hydrocarbons such as n-hexane, benzene, toluene and the like; amides such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide and the like; nitriles such as acetonitrile, propionitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; sulfolane; hexamethylphosphoramide; and the like can be mentioned. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

In this reaction, alkali metal iodide such as sodium iodide, potassium iodide and the like may be added as a reaction promoter, in a proportion of generally 1 - 20 mol, preferably 1 - 10 mol, per 1 mol of compound (BIII).

The amount of the compound (BIV) to be used is generally 1 - 10 mol, preferably 1 - 3 mol, per 1 mol of compound (BIII).

The reaction temperature is generally -80°C - 200°C, preferably 0°C - 150°C.

The reaction time is generally 10 min - 48 hr, preferably 15 min - 24 hr.

The compound (BIV) can be produced by the below-mentioned reaction.

[0247]

step 3

compound (BIa) can be produced by a method known per se,

for example, the method described in Reductions in Organic Chemistry Second Edition, American Chemical Society (1996), pp. 187-189; Journal of Chemical Society Perkin Transactions 1, (2000), pp. 145-146 and the like, or a method analogous thereto, by subjecting compound (BV) and compound (BIV) to reductive amination reaction.

Compound (BV) can be produced by the below-mentioned reaction.

[0248]

step 4

Compound (BVII) can be produced, for example, by reacting compound (BIII) with compound (BVI) in the presence of a base according to the production method of compound (BIa) from compound (BIII).

As compound (BVI), a commercially available product can be used, or it can be produced from a commercially available compound by a method known per se or a method analogous thereto.

[0249]

step 5

Compound (BVII) can be produced by subjecting compound (BV) and compound (BVI) to a reductive amination reaction according to the production method of, for example, compound (BIa) from compound (BV).

[0250]

step 6

Compound (BVIII) can be produced by hydrolysis of the ester of compound (BVII) by a method known per se, for example, the method described in Protective Groups in Organic Synthesis, Third Edition, Wiley-Interscience (1999) or a method analogous thereto.

[0251]

step 7

Compound (BIa) can be produced by, for example, condensing compound (BVIII) and compound (BIX).

The condensation reaction can be performed according to a conventional method, for example, a general peptide coupling method. Examples of such method include a method including directly condensing compound (BVIII) and compound (BIX) using a condensation agent, or a method including reacting a reactive derivative of compound (BVIII) with compound (BIX) and the like.

Examples of the condensation agent include carbodiimide condensation reagents such as dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIPC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and hydrochloride thereof and the like; phosphoric acid condensation reagents such as diethyl cyanophosphate, diphenylphosphoryl azide and the like; carbonyldiimidazole, 2-chloro-1,3-dimethylimidazolium tetrafluoroborate, O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) and the like.

Examples of the solvent to be used for direct condensation using a condensation agent include amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethyl sulfoxide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aliphatic hydrocarbons such as hexane, heptane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane, tert-butyl methyl ether and the like; esters such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; nitriles such as acetonitrile, propionitrile and the like; water; and the like. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

The amount of the condensation agent to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (BVIII).

When carbodiimide condensation reagent is used as the condensation agent, the reaction efficiency can be improved by the use of a suitable condensation promoter (e.g., 1-hydroxy-7-azabenzotriazole, 1-hydroxybenzotriazole, N-hydroxysuccinimide, N-hydroxyphthalimide) as necessary.

When HATU or phosphoric acid condensation reagent is used as the condensation agent, the reaction efficiency can be improved by the use of an organic amine base such as triethylamine, N,N-diisopropylethylamine and the like.

The amount of the condensation promoter or organic amine base to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (BVIII), respectively.

The amount of the compound (BIX) to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (BVIII).

The reaction time is generally 10 min - 60 hr, preferably 15 min - 24 hr.

The reaction temperature is generally -50 - 150°C, preferably -10 - 100°C.

[0252]

Examples of the reactive derivative of compound (BVIII) include acid halide (e.g., acid chloride, acid bromide), imidazolide, mixed acid anhydride (e.g., anhydrides with methyl carbonate, ethyl carbonate, isobutyl carbonate and the like) and the like.

When an acid halide is used as a reactive derivative of compound (BVIII), the reaction is generally performed in the presence of a base in a solvent inert to the reaction.

Examples of the base include amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, 4-dimethylaminopyridine and the like; alkali metal salts such as lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium hydrogen carbonate, sodium carbonate, potassium carbonate and the like; and the like.

The amount of the base to be used is generally 1 - 10 mol,

preferably 1 - 5 mol, per 1 mol of acid halide of compound (BVIII).

Examples of the solvent to be used for this reaction include amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethyl sulfoxide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aliphatic hydrocarbons such as hexane, heptane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane, tert-butyl methyl ether and the like; esters such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; nitriles such as acetonitrile, propionitrile and the like; water; and the like. These solvents may be used in a mixture at an appropriate ratio. When the above-mentioned amide is used as a solvent inert to the reaction, the reaction can also be performed in the absence of a base.

The amount of the compound (BIX) to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of acid halide of compound (BVIII).

The reaction temperature is generally -30°C - 150°C, preferably -10 - 100°C.

The reaction time is generally 10 min - 48 hr, preferably 15 min - 24 hr.

[0253]

When mixed acid anhydride is used as a reactive derivative of compound (BVIII), compound (BVIII) is reacted with chlorocarbonate (e.g., methyl chlorocarbonate, ethyl chlorocarbonate, isobutyl chlorocarbonate) in the presence of a base and then reacted with compound (BIX).

Examples of the base to be used for this reaction include those exemplified as the base to be used for the aforementioned reaction of acid halide of compound (BVIII) with compound (BIX).

The amount of the chlorocarbonate to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (BVIII).

The amount of the base to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (BVIII).

The amount of the compound (BIX) to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (BVIII).

The reaction temperature is generally -30°C - 120°C, preferably -10 - 100°C.

The reaction time is generally 10 min - 48 hr, preferably 15 min - 24 hr.

As compound (BIX), a commercially available product can be used, or it can be produced from a commercially available compound by a method known per se or a method analogous thereto.

[0254]

step 8

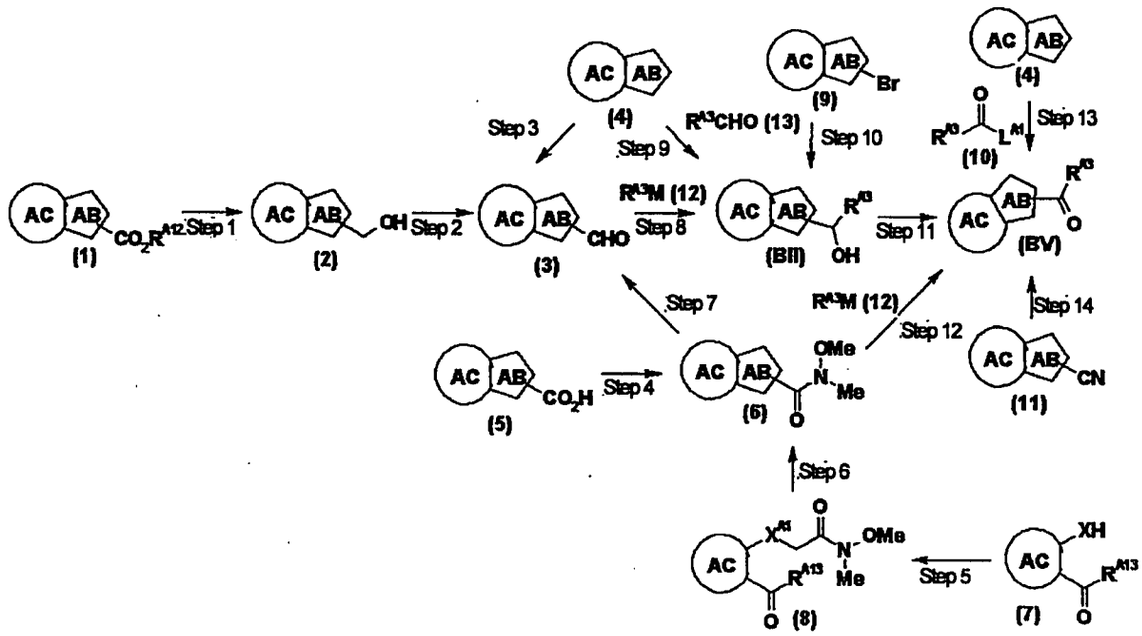
Compound (BIb) can be produced, for example, by hydrolyzing the ester of compound (BIa) according to the production method of compound (BVIII).

[0255]

Compound (BII) and compound (BV) which are starting material compounds of Reaction scheme A1 can be produced, for example, by the method shown in the following Reaction scheme A2.

Reaction scheme A2

[0256]




[0257]

wherein $X^{A1}$ is $NR^{A14}$, O, or S; $R^{A12}$ is a $C_{1-6}$ alkyl group; $R^{A13}$ and $R^{A14}$ are each independently a hydrogen atom, or a substituent that the aforementioned ring AB optionally has; $R^{A3}M$ is an organic metal compound (to be mentioned later); $L^{A1}$ is a leaving group (e.g., halogen atom such as chlorine, bromine and the like), and other symbols are as defined above.

step 1

Compound (2) can be produced by subjecting compound (1) to a reduction reaction. Reduction reaction can be performed according to a conventional method using a reducing agent.

Examples of the reducing agent include metal hydrogen compounds such as sodium bis(2-methoxyethoxy)aluminum hydride, diisobutylaluminum hydride (DIBALH) and the like; metal hydrogen complex compounds such as sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride, sodium aluminum hydride, calcium borohydride and the like; and the like.

The amount of the reducing agent to be used is generally 1 - 20 mol, preferably 1 - 10 mol, per 1 mol of compound (1).

This reaction is preferably performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, alcohols such

as methanol, ethanol, propanol, isopropanol, butanol, isobutanol, tert-butanol and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, trichloroethylene and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, dimethoxyethane and the like; water; and the like can be mentioned. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

The reaction time is generally 10 min - 48 hr, preferably 15 min - 24 hr.

The reaction temperature is generally -100°C - 150°C, preferably -20°C - 100°C.

As compound (1), a commercially available product can be used, or it can be produced from a commercially available compound by a method known per se or a method analogous thereto.

[0258]

step 2

Compound (3) can be produced, for example, by subjecting compound (2) to an oxidation reaction. The oxidation reaction can be performed according to a conventional method and using an oxidant.

Examples of the oxidant include active manganese dioxide, pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), Dess-Martin periodinane, dimethyl sulfoxide-acid anhydride (e.g., acetic anhydride, trifluoroacetic anhydride), dimethyl sulfoxide-thionyl chloride, dimethyl sulfoxide-sulfuryl chloride, dimethyl sulfoxide-oxalyl chloride, dimethyl sulfoxide-chlorine, and dimethyl sulfoxide-dicyclohexylcarbodiimide (DCC) in the presence of acid (e.g., phosphoric acid, trifluoroacetic acid, dichloroacetic acid) and the like.

The amount of the oxidant to be used is generally 1 - 100 mol, preferably 1 - 50 mol, per 1 mol of compound (2).

This reaction is preferably performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, ethers such as diethyl ether, diisopropyl ether, diphenylether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, tert-butylmethylether and the like; ketones such as acetone, methylethyl ketone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, trichloroethylene and the like; aromatic hydrocarbons such as benzene, toluene and the like; saturated hydrocarbons such as cyclohexane, hexane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoramide and the like; nitriles such as acetonitrile, propionitrile and the like; mineral acids such as hydrochloric acid, sulfuric acid and the like; organic acids such as formic acid, acetic acid, propionic acid, trifluoroacetic acid, methanesulfonic acid and the like, water; and the like can be mentioned. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

The reaction time is generally 10 min - 48 hr, preferably 15 min - 24 hr.

The reaction temperature is generally -100 - 150°C, preferably -20 - 100°C.

[0259]

step 3

Compound (3) can be produced by, for example, treating compound (4) with a base and reacting the compound with a formylation agent.

Examples of the base to be used for this reaction include, organic lithium compounds such as n-butyllithium, sec-butyllithium, tert-butyllithium and the like, and alkali amides such as lithium diisopropylamide, lithium

tris(trimethylsilyl)amide and the like.

The amount of the base to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (4).

Examples of the formylation agent include N,N-dimethylformamide, N-formylpiperidine, ethyl orthoformate and the like.

The amount of the formylation agent to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (4).

This reaction is preferably performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, ethers such as 1,4-dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether, ethylene glycol dimethylether and the like; hydrocarbons such as n-hexane, n-pentane and the like; and the like can be mentioned. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

The reaction time is generally 10 min - 48 hr, preferably 15 min - 24 hr.

The reaction temperature is generally -100 - 100°C, preferably -80 - 50°C.

As compound (4), a commercially available product can be used, or it can be produced from a commercially available compound by a method known per se or a method analogous thereto.

[0260]

step 4

compound (6) can be produced by condensing compound (5) and N,O-dimethylhydroxylamine according to the production method of, for example, compound (B1a) from compound (BVIII).

As compound (5), a commercially available product can be used, or it can be produced from a commercially available compound by a method known per se or a method analogous thereto.

[0261]

step 5

Compound (8) can be produced by reacting, for example, compound (7) with 2-chloro-N-methoxy-N-methylacetamide in the presence of a base according to the production method of compound (B1a) from compound (BIII).

As compound (7), a commercially available product can be used, or it can be produced from a commercially available compound by a method known per se or a method analogous thereto.

[0262]

step 6

Compound (6) can be produced, for example, by reacting compound (8) with a base.

Examples of the base include alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkaline earth metal hydroxides such as magnesium hydroxide, calcium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; alkali metal hydrogencarbonates such as sodium hydrogen carbonate, potassium hydrogen carbonate and the like; alkali metal alkoxides having 1 to 6 carbon atoms such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; metal hydrides such as sodium hydride, potassium hydride, calcium hydride and the like; organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) and the like; and the like.

The amount of the base to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (8).

This reaction is preferably performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, alcohols such as methanol, ethanol, 1-propanol, 2-propanol, tert-butyl alcohol and the like; ethers such as 1,4-dioxane,

tetrahydrofuran, diethyl ether, dimethoxyethane, tert-butyl methyl ether, diisopropyl ether, ethylene glycol dimethylether and the like; esters such as ethyl formate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, trichloroethylene and the like; hydrocarbons such as n-hexane, benzene, toluene and the like; amides such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide and the like; nitriles such as acetonitrile, propionitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; sulfolane; hexamethylphosphoramide; and the like can be mentioned. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -80°C - 200°C, preferably 0°C - 150°C.

The reaction time is generally 10 min - 48 hr, preferably 15 min - 24 hr.

[0263]

step 7

Compound (3) can be produced by subjecting, for example, compound (6) to a reduction reaction according to the production method of compound (2).

[0264]

step 8

compound (BII) can be produced by reacting, for example, compound (3) with organic metal compound (12).

Examples of the organic metal compound (12) include Grignard reagent (e.g., a compound represented by formula: $R^3MgBr$), organic lithium reagent (e.g., a compound represented by formula: $R^3Li$), organic zinc reagent (e.g., a compound represented by formula: $(R^3)_2Zn$), wherein $R^3$ is as defined above, and the like.

Such organic metal compound can be produced by a method known per se, for example, the method described in "Jikken Kagaku Kouza (The Chemical Society of Japan ed.), 4th Edition,

vol. 25, Synthesis by Organic Metal Reagent" pp. 9-449, Maruzen Press 1992, or a method analogous thereto.

The amount of the organic metal compound (12) to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (3).

This reaction is performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane and the like; aliphatic hydrocarbons such as hexane, heptane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; and the like can be mentioned. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

The reaction time is generally 10 min - 48 hr, preferably 15 min - 24 hr.

The reaction temperature is generally -100 - 200°C, preferably -80 - 150°C.

[0265]

step 9

Compound (BII) can be produced by, for example, treating compound (4) with a base, and reacting the compound with compound (13).

Examples of the base include those similar to the base described in step 3.

The amount of the base and compound (13) to be used is each generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (4).

This reaction is preferably performed in a solvent inert to the reaction. Examples of the solvent include those similar to the solvent described in step 3.

The reaction time is generally 10 min - 48 hr, preferably 15 min - 24 hr.

The reaction temperature is generally -100 - 100°C, preferably -80 - 50°C.

As compound (13), a commercially available product can be

used, or it can be produced from a commercially available compound by a method known per se or a method analogous thereto.

[0266]

step 10

Compound (BII) can be produced by treating, for example, compound (9) with a base, and then reacting the compound with compound (13).

Examples of the base include organic lithium compounds such as n-butyllithium, sec-butyllithium, tert-butyllithium and the like.

The amount of the base and compound (13) to be used is each generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (9).

This reaction is preferably performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, ethers such as 1,4-dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether, ethylene glycol dimethylether and the like; hydrocarbons such as n-hexane, n-pentane and the like; and the like can be mentioned. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

The reaction time is generally 10 min - 48 hr, preferably 15 min - 24 hr.

The reaction temperature is generally -100 - 100°C, preferably -80 - 50°C.

As compound (9), a commercially available product can be used, or it can be produced from a commercially available compound by a method known per se or a method analogous thereto.

[0267]

step 11

Compound (BV) can be produced, for example, by subjecting compound (BII) to an oxidation reaction according to step 2.

[0268]

step 12

Compound (BV) can be produced by reacting compound (6) with organic metal compound (12) according to, for example, step 8.

[0269]

step 13

Compound (BV) can be produced by Friedel-Crafts reaction of compound (4) and compound (10)

While this reaction is preferably performed by addition of an acid catalyst, where necessary, it may be performed without addition of an acid catalyst.

Examples of the acid catalyst to be used for the reaction include mineral acids such as sulfuric acid, anhydrous phosphoric acid, polyphosphoric acid and the like, Lewis acids such as aluminum chloride, tin tetrachloride, titanium tetrachloride, boron trifluoride, triethylaluminum, diethylaluminum chloride, zinc chloride and the like, and the like. Preferably, polyphosphoric acid, aluminum chloride, diethylaluminum chloride, zinc chloride and the like are used as acid catalysts.

An acid catalyst can be used in any equivalent amount, generally 0.1 - 50 mol, preferably 1 - 20 mol, per 1 mol of compound (4). In some cases, an acid catalyst can also be used as a solvent.

The amount of the compound (10) to be used is generally 1 - 20 mol, preferably 1 - 10 mol, per 1 mol of compound (4).

This reaction can be performed without solvent, or after dissolving or suspending in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, hydrocarbons such as n-hexane, benzene, toluene and the like; ethers such as 1,4-dioxane, tetrahydrofuran, diethyl ether, dimethoxyethane, tert-butyl methyl ether, diisopropyl ether, ethylene glycol dimethylether, 1,2-dichloroethane and the like; halogenated

hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, trichloroethylene and the like; nitrohydrocarbons such as nitromethane, nitrobenzene and the like; nitriles such as acetonitrile, propionitrile and the like; amides such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethyl sulfoxide and the like; sulfolane; hexamethylphosphoramide; carbon disulfide; and the like can be mentioned. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

The reaction time is generally 10 min - 48 hr, preferably 15 min - 24 hr.

The reaction temperature is generally -100 - 300°C, preferably 0 - 200°C.

As compound (10), a commercially available product can be used, or it can be produced from a commercially available compound by a method known per se or a method analogous thereto.

[0270]

step 14

Compound (BV) can be produced, for example, by reacting compound (11) with an organic metal reagent according to step 8.

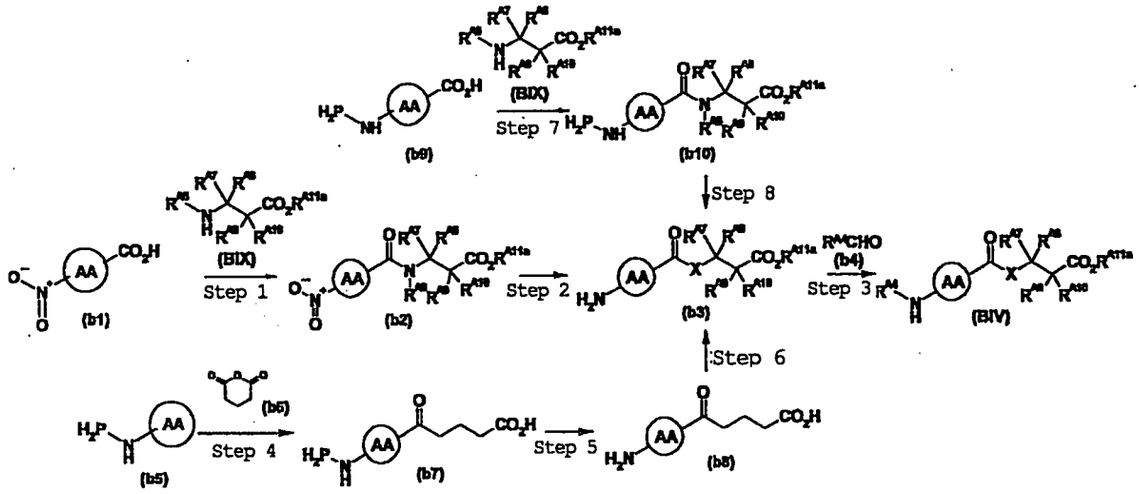
As compound (11), a commercially available product can be used, or it can be produced from a commercially available compound by a method known per se or a method analogous thereto.

[0271]

compound (BIV) which is a starting material compound in Reaction scheme A1 can be produced, for example, by a method shown in the following Reaction scheme A3.

Reaction scheme A3

[0272]




[0273]

wherein P is an amino-protecting group, and other symbols are each as defined above.

[0274]

step 1

Compound (b2) can be produced, for example, by condensing compound (b1) and compound (BIX) according to the production method of compound (B1a) from compound (BVIII).

As compound (b1), a commercially available product can be used, or it can be produced from a commercially available compound by a method known per se or a method analogous thereto.

[0275]

step 2

Compound (b3) can be produced by subjecting compound (b2) to a reduction reaction in the presence of a metal catalyst and a hydrogen source. Such reduction reaction can be performed according to a conventional method in a solvent that does not adversely influence the reaction.

Examples of the metal catalyst include palladium-carbon, palladium black, palladium chloride, platinum oxide, platinum black, platinum-palladium, Raney-nickel, Raney cobalt and the like.

Examples of the hydrogen source include hydrogen gas, formic acid, formic acid amine salt, phosphinate salt,

hydrazine and the like.

Examples of the solvent that does not adversely influence the reaction include methanol, tetrahydrofuran, N,N-dimethylacetamide and the like.

The amount of the metal catalyst to be used is generally 0.001 - 1000 mol, preferably 0.01 - 100 mol, per 1 mol of compound (b2).

The reaction temperature is generally -70 - 150°C, preferably -20 - 100°C.

The reaction time is generally 0.1 - 100 hr, preferably 0.1 - 40 hr.

This reaction can also be performed in the presence of a reducing agent in a solvent that does not adversely influence the reaction.

As the reducing agent, ferric oxide, zinc, tin and the like can be mentioned, and compound (b3) can be produced according to the reaction described in "Jikken Kagaku Kouza (The Chemical Society of Japan ed.), 4th Edition, vol. 20. Organic Synthesis II Alcohol and Amine" pp. 279-280, Maruzen Press 1992, or a method analogous thereto.

The amount of the reducing agent to be used is generally 0.1 - 20 mol per 1 mol of compound (b2).

Examples of the solvent that does not adversely influence the reaction include alcohols such as methanol, ethanol, propanol, isopropanol, butanol, isobutanol, tert-butanol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, dimethoxyethane and the like; esters such as methyl acetate, ethyl acetate, n-butyl acetate, tert-butyl acetate and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; and the like. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -70 - 150°C, preferably -20 - 100°C.

The reaction time is generally 0.1 - 100 hr, preferably 0.1 - 40 hr.

[0276]

step 3

Compound (BIV) can be produced by, for example, reductive amination reaction of compound (b3) and compound (b4) according to the production method of compound (B1a) from compound (BV).

As compound (b4), a commercially available product can be used, or it can be produced from a commercially available compound by a method known per se or a method analogous thereto.

[0277]

step 4

Compound (b7) can be produced by Friedel-Crafts reaction of compound (b5) and glutaric anhydride (b6) by the synthesis method described in WO2004/45616 or a method analogous thereto.

As compound (b5), a commercially available product can be used, or it can be produced from a commercially available compound by a method known per se or a method analogous thereto.

[0278]

step 5

Compound (b8) can be produced by removing the protecting group from compound (b7) by a method known per se, for example, the method described in Protective Groups in Organic Synthesis, Third Edition, Wiley-Interscience (1999) or a method analogous thereto.

[0279]

step 6

Compound (b3) ($R^{A7}$, $R^{A8}$, $R^{A9}$ and $R^{A10}$ are hydrogen atoms) can be produced by esterification of compound (b8) by a method known per se, for example, the method described in Protective

Groups in Organic Synthesis, Third Edition, Wiley-Interscience (1999) or a method analogous thereto.

[0280]

step 7

Compound (b10) can be produced, for example, by condensing compound (b9) and compound (BIX) according to the production method of compound (B1a) from compound (BVIII).

As compound (b9), a commercially available product can be used, or it can be produced from a commercially available compound by a method known per se or a method analogous thereto.

[0281]

step 8

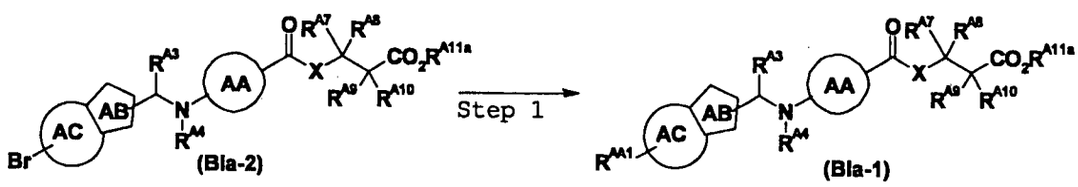
Compound (b3) can be produced, for example, by removing the protecting group from compound (b10) according to the method of step 5.

[0282]

Of compounds (IA), a compound represented by the following formula (BIa-1) [compound (BIa-1)] can be produced according to the following Reaction scheme A4.

Reaction scheme A4

[0283]




[0284]

wherein $R^{AA1}$ is a $C_{1-6}$ alkyl group, a $C_{6-14}$ aryl group, a 4- to 12-membered aromatic heterocyclic group (group bonded via a carbon atom on the ring), a 4- to 12-membered nonaromatic heterocyclic group (group bonded via a carbon atom on the ring), or a cyano group, and other symbols are as defined above.

[0285]

step 1

Compound (BIa-1) can be produced, for example, by reacting compound (BIa-2) with an organic metal reagent or metal cyanide in the presence of a metal catalyst.

Examples of the metal catalyst include palladium catalyst (e.g., palladium (II) acetate, tris(dibenzylideneacetone)dipalladium (0), bis(dibenzylideneacetone)palladium (0), tetrakis(triphenylphosphine)palladium (0), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) dichloromethane adduct, bis(tris-tert-butylphosphine)palladium (0) etc.); nickel catalyst (e.g., tetrakis(triphenylphosphine)nickel (0), dichloro[1,2-bis(diphenylphosphino)ethane]nickel (II), dichloro[1,3-bis(diphenylphosphino)propane]nickel (II), dichloro[1,4-bis(diphenylphosphino)butane]nickel (II) etc.).

The amount of the metal catalyst to be used is generally 0.01 - 1 mol, preferably 0.03 - 0.5 mol, per 1 mol of compound (BIa-2).

[0286]

Examples of the organic metal reagent include boronic acid, boronate ester, Grignard reagent, organotin reagent, organozinc reagent and the like.

Examples of the metal cyanide include zinc cyanide and the like.

The amount of the organic metal reagent or metal cyanide to be used is generally 1 - 100 mol, preferably 1 - 10 mol, per 1 mol of compound (BIa-2).

[0287]

This reaction may be performed in the presence of a base as necessary.

Examples of such base include alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkaline earth metal hydroxides such as magnesium hydroxide, calcium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate,

cesium carbonate and the like; alkali metal hydrogencarbonates such as sodium hydrogen carbonate, potassium hydrogen carbonate and the like; alkali metal alkoxide having a carbon number of 1 to 6 such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like. and the like.

The amount of the base to be used is generally 1 - 100 mol, preferably 1 - 10 mol, per 1 mol of compound (BIa-2).

[0288]

This reaction may be performed in the presence of a ligand as necessary.

Examples of such ligand include phosphorus ligand (e.g., triphenylphosphine, 1,3-bis(diphenylphosphino)propane, 1,3-bis(diphenylphosphino)propane, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene etc.).

The amount of the ligand to be used is generally 0.01 - 2 mol, preferably 0.02 - 1 mol, per 1 mol of compound (BIa-2).

[0289]

This reaction is preferably performed in a solvent inert to the reaction.

Such solvent is not particularly limited as long as the reaction proceeds and, for example, alcohols such as methanol, ethanol, propanol, isopropanol, butanol, tert-butanol and the like; ethers such as 1,4-dioxane, tetrahydrofuran, diethyl ether, dimethoxyethane, tert-butyl methyl ether, diisopropyl ether, ethylene glycol dimethylether and the like; esters such as ethyl formate, ethyl acetate, n-butyl acetate and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, trichloroethylene and the like; hydrocarbons such as n-hexane, benzene, toluene and the like; amides such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide and the like; nitriles such as acetonitrile, propionitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; sulfolane; hexamethylphosphoramide; water and the like can be mentioned. Two or more kinds of

these solvents may be used in a mixture at an appropriate ratio.

[0290]

The reaction temperature is generally -100 - 180°C, preferably -80°C - 150°C.

The reaction time is generally 0.1 hr - 48 hr, preferably 0.1 hr - 24 hr.

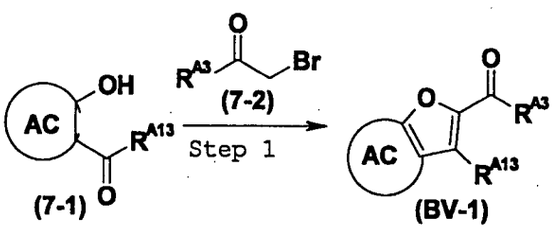
Compound (BIa-2) can be produced, for example, according to the production method of compound (BIa) in Reaction scheme A1.

[0291]

Of compounds (BV) described in Reaction scheme A2, a compound represented by the following formula (BV-1) [compound (BV-1)] can be produced according to the following Reaction scheme A5.

Reaction scheme A5

[0292]




[0293]

wherein each symbol is as defined above.

[0294]

step 1

Compound (BV-1) can be produced, for example, by reacting compound (7-1) with compound (7-2) in the presence of a base.

Examples of the base include alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkaline earth metal hydroxides such as magnesium hydroxide, calcium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; alkali metal hydrogencarbonates such as sodium hydrogen carbonate, potassium hydrogen

carbonate and the like; alkali metal alkoxides having 1 to 6 carbon atoms such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; metal hydrides such as sodium hydride, potassium hydride and calcium hydride; organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) and the like, and the like.

The amount of the base to be used is generally 1 - 50 mol, preferably 1 - 20 mol, per 1 mol of compound (7-1).

The amount of the compound (7-2) to be used is generally 1 - 10 mol, preferably 1 - 5 mol, per 1 mol of compound (7-1).

[0295]

This reaction is preferably performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, alcohols such as methanol, ethanol, 1-propanol, 2-propanol, tert-butyl alcohol and the like; ethers such as 1,4-dioxane, tetrahydrofuran, diethyl ether, dimethoxyethane, tert-butyl methyl ether, diisopropyl ether, ethylene glycol dimethylether and the like; esters such as ethyl formate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, trichloroethylene and the like; hydrocarbons such as n-hexane, benzene, toluene and the like; amides such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide and the like; nitriles such as acetonitrile, propionitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; sulfolane; hexamethylphosphoramide and the like can be mentioned. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

[0296]

The reaction temperature is generally -80°C - 200°C, preferably 0°C - 150°C.

The reaction time is generally 10 min - 48 hr, preferably 15 min - 24 hr.

Compound (7-1) can be produced by a method known per se or a method analogous thereto.

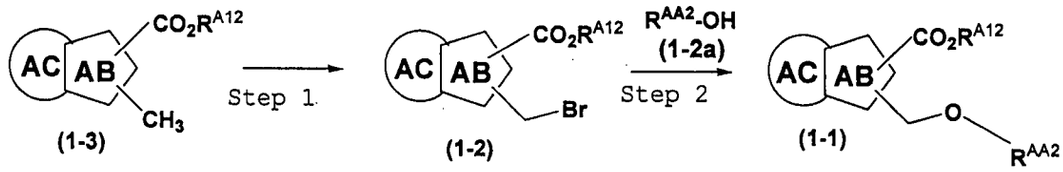
Compound (7-2) can be produced by a method known per se or a method analogous thereto.

[0297]

Of compounds (1), a compound represented by the following formula (1-1) [compound (1-1)] can be produced according to the following Reaction scheme A6.

Reaction scheme A6

[0298]




[0299]

wherein $R^{AA2}$ is a $C_{1-6}$ alkyl group, and other symbols are as defined above.

[0300]

step 1

Compound (1-2) can be produced, for example, by bromination of compound (1-3).

Examples of the bromination reagent include N-bromoamides such as N-bromosuccinimide, 1,3-dibromo-5,5-dimethylhydantoin and the like.

The amount of the bromination reagent to be used is generally 1 - 100 mol, preferably 1 - 10 mol, per 1 mol of compound (1-3).

This reaction may be performed in the co-presence of a radical initiator when desired.

Examples of such radical initiator include azobisisobutyronitrile, benzoyl peroxide and the like.

The amount of the radical initiator to be used is generally 0.001 - 10 mol, preferably 0.01 - 5 mol, per 1 mol of compound (1-3).

This reaction is preferably performed in a solvent inert

to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, esters such as ethyl formate, ethyl acetate, n-butyl acetate and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, trichloroethylene and the like; nitriles such as acetonitrile, propionitrile and the like and the like can be mentioned. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

[0301]

The reaction temperature is generally -100 - 180°C, preferably -80°C - 150°C.

The reaction time is generally 0.1 hr - 48 hr, preferably 0.1 hr - 24 hr.

Compound (1-3) can be produced by a method known per se or a method analogous thereto.

[0302]

step 2

Compound (1-1) can be produced, for example, by reacting compound (1-2) with an alkali metal alkoxide.

Alternatively, compound (1-1) can also be produced, for example, by reacting compound (1-2) with compound (1-2a) in the presence of a base.

[0303]

Examples of the alkali metal alkoxide include sodium methoxide, potassium methoxide, sodium ethoxide, potassium ethoxide and the like.

The amount of the alkali metal alkoxide to be used is generally 1 - 50 mol, preferably 1 - 10 mol, per 1 mol of compound (1-2).

Examples of the base include alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; alkali metal hydrogencarbonates such as sodium hydrogen carbonate, potassium hydrogen carbonate and the like; metal hydrides such as sodium hydride, potassium hydride and calcium hydride, and the like.

The amount of the base to be used is generally 1 - 50 mol, preferably 1 - 10 mol, per 1 mol of compound (1-2).

The amount of the compound (1-2a) to be used is generally 1 - 50 mol, preferably 1 - 10 mol, per 1 mol of compound (1-2).

This reaction is preferably performed in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds and, for example, alcohols such as methanol, ethanol, 1-propanol, 2-propanol, tert-butyl alcohol and the like; ethers such as 1,4-dioxane, tetrahydrofuran, diethyl ether, dimethoxyethane, tert-butyl methyl ether, diisopropyl ether, ethylene glycol dimethylether and the like; esters such as ethyl formate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, trichloroethylene and the like; hydrocarbons such as n-hexane, benzene, toluene and the like; amides such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide and the like; nitriles such as acetonitrile, propionitrile and the like; sulfoxides such as dimethyl sulfoxide and the like; sulfolane; hexamethylphosphoramide and the like can be mentioned. Two or more kinds of these solvents may be used in a mixture at an appropriate ratio.

In this reaction, alkali metal iodides such as sodium iodide, potassium iodide and the like may be added as a reaction promoter in an amount of generally 1 - 50 mol, preferably 1 - 10 mol, per 1 mol of compound (1-2).

The reaction temperature is generally -80°C - 200°C, preferably 0°C - 150°C. The reaction time is generally 0.1 hr - 48 hr, preferably 0.1 hr - 24 hr.

Compound (1-2a) can be produced by a method known per se or a method analogous thereto.

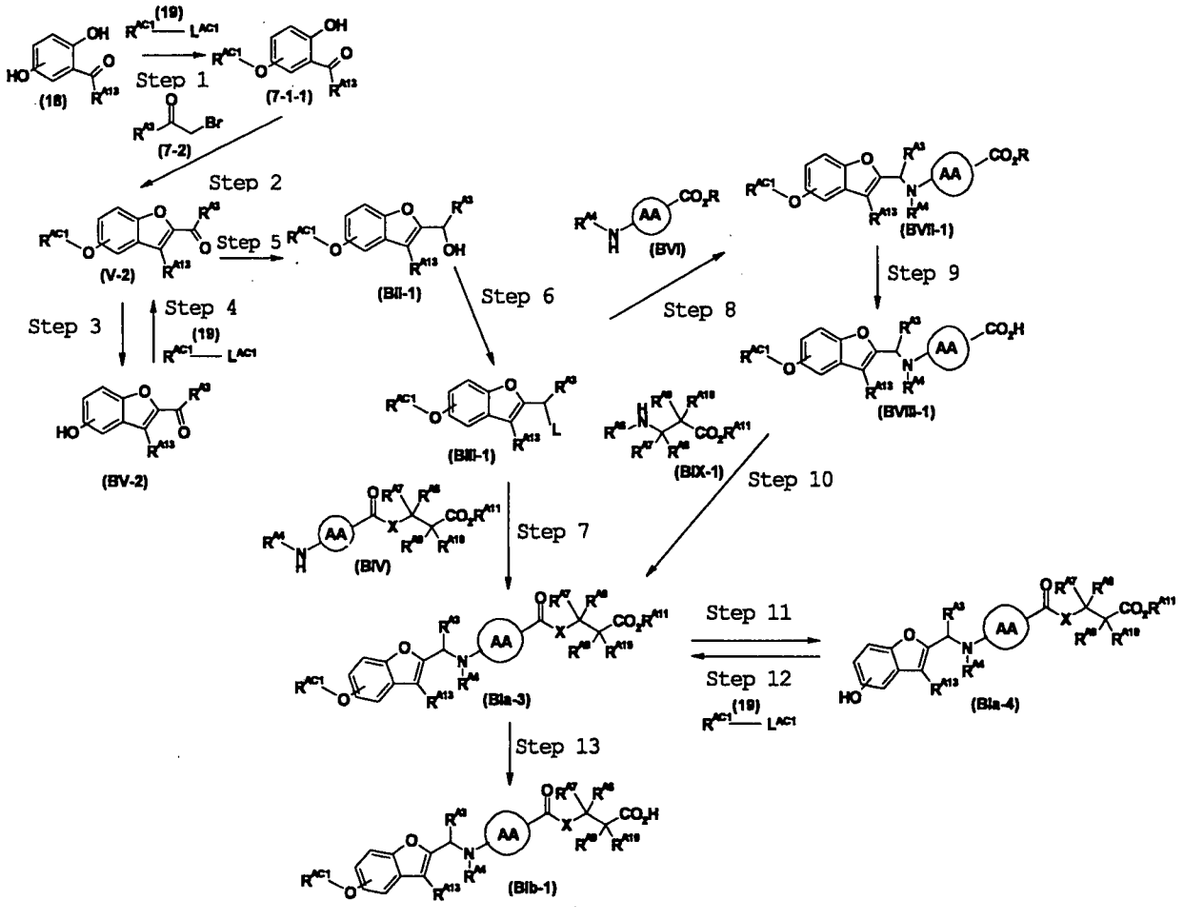
[0304]

In compound (BIa) of Reaction scheme A1, a compound represented by the following formula (BIa-3) [compound (BIa-3)] and a compound represented by the formula (BIa-4)

[compound (BIa-4)], and in compound (BIb) of Reaction scheme A1, a compound represented by the following formula (BIb-1) [compound (BIb-1)] can be produced, for example, by the methods shown in the following Reaction scheme A7.

Reaction scheme A7

[0305]




[0306]

wherein $R^{AC1}$ is

(1) $C_{1-6}$ alkyl optionally substituted by 1 to 3 substituents selected from

(a) halogen atom,

(b) carboxy group,

(c) $C_{1-6}$ alkoxy group,

(d) $C_{3-6}$ cycloalkyl group,

(e) $C_{1-6}$ alkoxy-carbonyl group optionally substituted by 1 to 3 $C_{6-14}$ aryl groups,

(f) amino group optionally mono- or di-substituted by

substituent(s) selected from $C_{1-6}$ alkyl group and $C_{1-6}$ alkoxy-carbonyl group,

(g) 4- to 12-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from

(i) halogen atom, and

(ii) $C_{1-6}$ alkyl group,

(h) 4- to 12-membered nonaromatic heterocyclic group optionally substituted by 1 to 3 $C_{1-6}$ alkyl groups,

(i) $C_{1-6}$ alkylsulfonyl group,

(j) $C_{1-6}$ alkylthio group, and

(k) hydroxy group;

(2) $C_{7-13}$ aralkyl group;

(3) $C_{6-14}$ aryl group;

(4) $C_{1-6}$ alkyl-carbonyl group;

(5) 4- to 12-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from

(i) $C_{1-6}$ alkyl group optionally substituted by 1 to 3 halogen atoms, and

(ii) cyano group;

(6) 4- to 12-membered non-aromatic heterocyclyl-oxy group,

$L^{AC1}$ is a leaving group or a hydroxy group,

and other symbols are as defined above.

Examples of the "leaving group" for $L^{AC1}$ include fluorine atom, chlorine atom, bromine atom, iodine atom, benzenesulfonyloxy group, p-toluenesulfonyloxy group, methanesulfonyloxy group, trifluoromethanesulfonyloxy group and the like.

[0307]

step 1

In this step, for example, compound (7-1-1) can be produced by reacting compound (18) with compound (19).

When $L^{AC1}$ is a leaving group, this reaction is performed in the presence of a base in a solvent that does not adversely influence the reaction.

Examples of the base include amines such as triethylamine,

N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydrogen carbonate, sodium carbonate, potassium carbonate, tripotassium phosphate and the like; alkali metal hydroxide such as sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; alkaline earth metal hydroxide such as magnesium hydroxide, calcium hydroxide, barium hydroxide and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal $C_{1-6}$ alkoxide such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like, and the like.

The amount of the base to be used is generally 1 - 1000 mol, preferably 1 - 5 mol, per 1 mol of compound (18).

The amount of the compound (19) to be used is generally 1 - 1000 mol, preferably 1 - 10 mol, per 1 mol of compound (18).

Examples of the solvent that does not adversely influence the reaction include ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethyl sulfoxide and the like; ketones such as acetone and the like; acetonitrile; water. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -80°C to 150°C, preferably -10°C to 100°C.

The reaction time is generally 0.5 - 20 hr.

[0308]

When $L^{AC1}$ is a hydroxy group, this reaction is performed by a method known per se, for example, the method described in Synthesis, page 1 (1981), or a method analogous thereto. That is, this reaction is performed generally in the presence of an organic phosphorus compound and electrophile in a solvent that does not adversely influence the reaction.

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Examples of the organic phosphorus compound include triphenylphosphine, tributylphosphine and the like.

Examples of the electrophile include diethyl azodicarboxylate, diisopropyl azodicarboxylate, 1,1'-azodicarbonyldipiperidine and the like.

The amount of the organic phosphorus compound and electrophile to be used is each generally 1 - 1000 mol, preferably 1 - 5 mol, per 1 mol of compound (18).

The amount of the compound (19) to be used is generally 1 - 1000 mol, preferably 1 - 5 mol, per 1 mol of compound (18).

As the solvent that does not adversely influence the reaction, those similar to the aforementioned can be mentioned.

The reaction temperature is generally -80 - 150°C, preferably -10 - 100°C.

[0309]

Compound (18) and compound (19) can be each produced according to a method known per se.

[0310]

step 2

In this step, for example, compound (7-1-1) is reacted with compound (7-2) in the presence of a base to give compound (V-2).

This reaction is performed in the same manner as in Reaction scheme A5, step 1.

Compound (7-2) can be produced according to a method known per se.

[0311]

step 3

In this step, for example, $R^{AC1}$ of compound (V-2) is removed to give compound (BV-2).

When $R^{AC1}$ is a benzyl group, this reaction can be performed, for example, in the presence of a metal catalyst such as palladium-carbon, palladium black, palladium-carbon ethylenediamine complex, palladium chloride, platinum oxide, platinum black, platinum-palladium, Raney-nickel, Raney cobalt

and the like and a hydrogen source in a solvent that does not adversely influence the reaction.

The amount of the metal catalyst to be used is generally 0.001 - 1000 mol, preferably 0.01 - 100 mol, per 1 mol of compound (V-2).

Examples of the hydrogen source include hydrogen gas, formic acid, formic acid amine salt, phosphinate salt, hydrazine and the like.

Examples of the solvent that does not adversely influence the reaction include alcohols such as methanol, ethanol, propanol, 2-propanol, 2-methoxyethanol, butanol, isobutanol, tert-butanol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; ethyl acetate, acetic acid and the like. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 - 120°C, preferably 10 - 80°C.

The reaction time is generally 0.5 - 100 hr.

[0312]

step 4

In this step, for example, compound (V-2) can be produced by reacting compound (BV-2) with compound (19). This step is performed in the same manner as in this reaction, step 1.

[0313]

step 5

In this step, for example, compound (BII-1) can be produced by subjecting compound (V-2) to a reduction reaction. This reaction is performed in the same manner as in Reaction

scheme 1, step 1.

[0314]

step 6

In this step, for example, compound (BIII-1) can be produced by converting the hydroxy group of compound (BII-1) to leaving group (L). This reaction is performed in the same manner as in Reaction scheme A1, step 1.

[0315]

step 7

In this step, for example, compound (BIa-3) can be produced by reacting compound (BIII-1) with compound (BIV) in the presence of a base. This reaction is performed in the same manner as in Reaction scheme A1, step 2.

[0316]

step 8

In this step, for example, compound (BVII-1) can be produced by reacting compound (BIII-1) with compound (BVI) in the presence of a base. This reaction is performed in the same manner as in Reaction scheme A1, step 4.

[0317]

step 9

In this step, for example, compound (BVIII-1) can be produced by hydrolyzing the ester of compound (BVII-1). This reaction is performed in the same manner as in Reaction scheme A1, step 6.

[0318]

step 10

In this step, for example, compound (BIa-3) can be produced by condensing compound (BVIII-1) and compound (BIX-1). This reaction is performed in the same manner as in Reaction scheme A1, step 7.

As compound (BIX-1), a commercially available product can be used, or it can be produced from a commercially available compound by a method known per se or a method analogous thereto.

[0319]

step 11

In this step, for example, compound (BIa-4) can be produced by removing $R^{AC1}$ from compound (BIa-3). This step is performed in the same manner as in this reaction, step 3.

[0320]

step 12

In this step, for example, compound (BIa-3) can be produced by reacting (BIa-4) with compound (19). This step is performed in the same manner as in this reaction, step 1.

[0321]

step 13

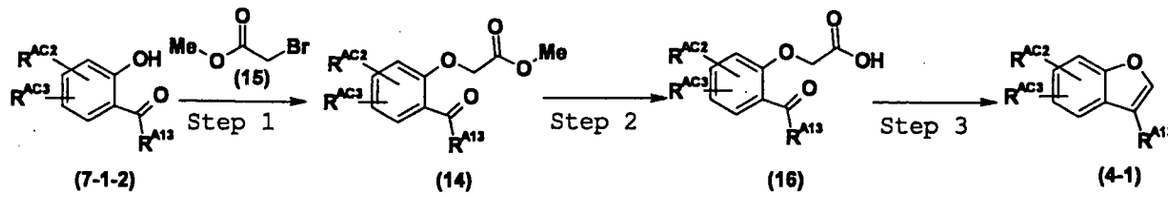
In this step, for example, compound (BIb-1) can be produced by hydrolyzing the ester of compound (BIa-3) according to the production method of compound (BVIII).

[0322]

Compound (4-1) which is a starting material compound of Reaction scheme A2 can be produced, for example, according to the method shown in the following Reaction scheme A8.

Reaction scheme A8

[0323]




[0324]

wherein $R^{AC2}$ and $R^{AC3}$ are each a substituent that the aforementioned ring AC optionally has, and other symbols are as defined above.

[0325]

step 1

In this step, for example, compound (14) can be produced by reacting compound (7-1-2) with compound (15) under basic conditions. This reaction is performed in the same manner as in Reaction scheme A5, step 1.

[0326]

step 2

In this step, for example, compound (16) can be produced by hydrolyzing the ester of compound (14) according to the production method of compound (BVIII) in Reaction scheme A1.

[0327]

step 3

In this step, for example, compound (4-1) can be produced by reacting compound (16) in acetic anhydride.

In this step, sodium acetate may be used as an additive.

The amount of sodium acetate to be used is generally 1 - 1000 mol, preferably 1 - 10 mol, per 1 mol of compound (16).

The reaction temperature is generally -80 - 200°C, preferably -10 - 150°C.

The reaction time is generally 0.5 - 20 hr.

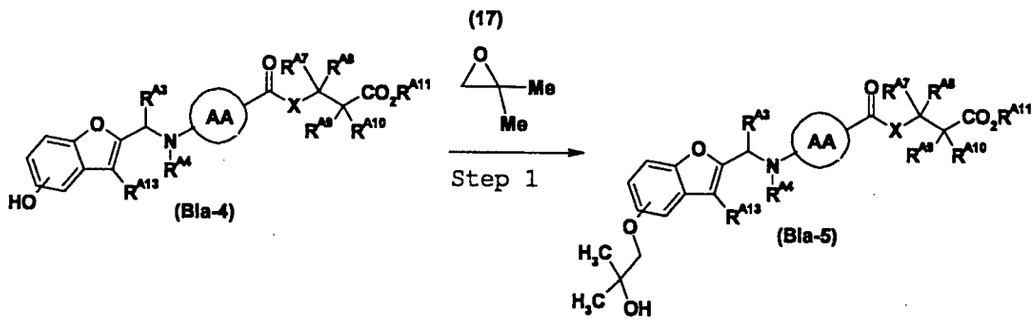
Compound (7-1-2) and compound (15) can be produced according to a method known per se.

[0328]

In compound (BIa-3) of Reaction scheme A7, a compound represented by the following formula (BIa-5) [compound (BIa-5)] can be produced, for example, by the method shown in the following Reaction scheme A9.

Reaction scheme A9

[0329]




[0330]

wherein the symbols are as defined above.

[0331]

step 1

In this step, for example, compound (BIa-5) can be produced by reacting compound (BIa-4) with compound (17).

This reaction is performed in the presence of a base in a solvent that does not adversely influence the reaction.

Examples of the base include amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydrogen carbonate, sodium carbonate, potassium carbonate and the like; alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; alkaline earth metal hydroxides such as magnesium hydroxide, calcium hydroxide, barium hydroxide and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal $C_{1-6}$ alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like, and the like.

The amount of the base to be used is generally 1 - 50 mol, preferably 1 - 5 mol, per 1 mol of compound (BIa-4).

The amount of the compound (17) to be used is generally 1 - 50 mol, preferably 1 - 5 mol, per 1 mol of compound (BIa-4).

In this reaction, sodium iodide or potassium iodide may be further added to the solvent.

The amount of sodium iodide or potassium iodide to be used is generally 1 - 100 mol, preferably 1 - 10 mol, per 1 mol of compound (BIa-4).

Examples of the solvent that does not adversely influence the reaction include ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; ketones such as acetone and the like; acetonitrile; water. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 - 150°C,

preferably 0 - 100°C.

The reaction time is generally 0.5 - 100 hr.

Compound (BIa-4) can be produced according to Reaction scheme A7.

Compound (17) can be produced according to a method known per se.

[0332]

The thus-obtained compound (I) and compound (IA) can be isolated and purified by known separation and purification means, for example, concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

In addition, when compound (I) and compound (IA) are obtained as free compounds, they can be converted to object salts by a method known per se or a method analogous thereto. When they are obtained as salts, they can be converted to free forms or other object salts by a method known per se or a method analogous thereto.

When compound (I) or compound (IA) contains an optical isomer, a stereoisomer, a regioisomer or a rotamer, these are also encompassed in compound (I) and compound (IA), and can be obtained as a single product according to synthesis and separation methods known *per se*. For example, when compound (I) and compound (IA) have an optical isomer, an optical isomer resolved from this compound is also encompassed in compound (I) and compound (IA).

The optical isomer can be prepared according to a method known per se. To be specific, an optically active synthetic intermediate is used, or the final racemate product is subjected to optical resolution according to a conventional method to give an optical isomer.

The method of optical resolution may be a method known *per se*, such as a fractional recrystallization method, a chiral column method, a diastereomer method etc.

1) Fractional recrystallization method

A method wherein a salt of a racemate with an optically active compound (e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine etc.) is formed, which is separated by a fractional recrystallization method, and if desired, a neutralization step to give a free optical isomer.

2) Chiral column method

A method wherein a racemate or a salt thereof is applied to a column for separation of an optical isomer (a chiral column) to allow separation. In the case of a liquid chromatography, for example, a mixture of the optical isomers is applied to a chiral column such as ENANTIO-OVM (manufactured by Tosoh Corporation), CHIRAL series (manufactured by Daicel Chemical Industries, Ltd.) and the like, and developed with water, various buffers (e.g., phosphate buffer, etc.) and organic solvents (e.g., ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine etc.) solely or in admixture to separate the optical isomer. In the case of a gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (manufactured by GL Sciences Inc.) and the like is used to allow separation.

3) Diastereomer method

A method wherein a racemic mixture is prepared into a diastereomeric mixture by chemical reaction with an optically active reagent, which is made into a single substance by a typical separation means (e.g., a fractional recrystallization method, a chromatography method etc.) and the like, and is subjected to a chemical treatment such as hydrolysis and the like to separate an optically active reagent moiety, whereby an optical isomer is obtained. For example, when compound (I) or compound (IA) contains hydroxy, or primary or secondary amino group within a molecule, the compound and an optically active organic acid (e.g., MTPA [α-methoxy-α-

(trifluoromethyl)phenylacetic acid],
(-)-menthoxyacetic acid etc.) and the like are subjected to condensation reaction to give diastereomers of the ester compound or the amide compound, respectively. When compound (I) has a carboxyl group, this compound and an optically active amine or an optically active alcohol are subjected to condensation reaction to give diastereomers of the amide compound or the ester compound, respectively. The separated diastereomer is converted to an optical isomer of the original compound by acid hydrolysis or base hydrolysis.

Examples

[0333]

The present invention is explained in more detail in the following by referring to Examples, Experimental Examples and Formulation Examples, which are not to be construed as limitative.

[0334]

$^1$H-NMR spectrum was measured using tetramethylsilane as the internal standard and Varian Gemini 200 (200 MHz), 300 (300 MHz), Bruker 300 (300 MHz) spectrometers, and all δ values are shown by ppm. Unless otherwise specified, the numerical values shown for mixed solvents are volume mixing ratios of respective solvents. Unless otherwise specified, % means weight%. In addition, unless otherwise specified, the ratio of elution solvents in silica gel chromatography means a volume mixing ratio. The room temperature (ambient temperature) in the present specification is a temperature of about 20°C to about 30°C.

[0335]

Each symbol in the Examples means the following.

DMSO: dimethyl sulfoxide,

$CDCl_3$: deuterated chloroform ,

s: singlet,

d: doublet,

t: triplet,

q: quartet,

dd: double doublet,

dt: double triplet,

quint: quintet,

m: multiplet,

brs: broad,

J: coupling constant

[0336]

LC/MS analyses in Examples were performed under the following conditions.

measurement device: Waters LC/MS system

HPLC: Agilent HP1100

MS: Micromass ZMD

column: CAPCELL PAK c18UG120 S-3 μm, 1.5×35 mm (manufactured by Shiseido Co., Ltd.)

solvent: SOLUTION A; 0.05% aqueous trifluoroacetic acid solution, SOLUTION B; 0.04% trifluoroacetic acid acetonitrile solution

gradient cycle: 0 min. (SOLUTION A/SOLUTION B=90/10), 2.00 min. (SOLUTION A/SOLUTION B=5/95), 2.75 min. (SOLUTION A/SOLUTION B=5/95), 2.76 min. (SOLUTION A/SOLUTION B=90/10), 3.60 min. (SOLUTION A/SOLUTION B=90/10)

injection volume: 2 μL,

flow rate: 0.5 mL/min,

detection method: UV 220 nm,

MS conditions ionization method: ESI

[0337]

Purification by preparative HLPC in Examples was performed under the following conditions.

instrument: Gilson Inc., High throughput purification system

column: YMC CombiPrep ODS-A S-5 μm, 50×20 mm, or CombiPrep Hydrosphere C18 S-5 μm, 50×20 mm

solvent: SOLUTION A; 0.1% aqueous trifluoroacetic acid solution, SOLUTION B; 0.1% trifluoroacetic acid acetonitrile solution

gradient cycle: 0 min. (SOLUTION A/SOLUTION B=95/5), 1.00 min. (SOLUTION A/SOLUTION B=95/5), 5.20 min. (SOLUTION A/SOLUTION B=5/95), 6.40 min. (SOLUTION A/SOLUTION B=5/95), 6.50 min. (SOLUTION A/SOLUTION B=95/5), 6.60 min. (SOLUTION A/SOLUTION B=95/5), or 0 min. (SOLUTION A/SOLUTION B=98/2), 1.00 min. (SOLUTION A/SOLUTION B=98/2), 5.00 min. (SOLUTION A/SOLUTION B=0/100), 6.40 min. (SOLUTION A/SOLUTION B=0/100), 6.50 min. (SOLUTION A/SOLUTION B=98/2), 6.60 min. (SOLUTION A/SOLUTION B=98/2)

flow rate: 20 mL/min,

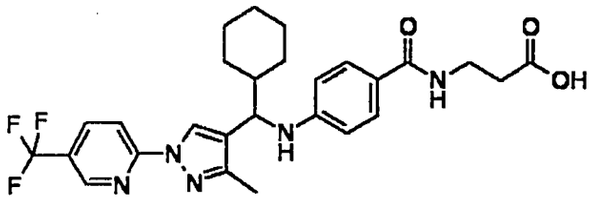
detection method: UV 220 nm

[0338]

Example 1

3-[({4-[(cyclohexyl{3-methyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[0339]



[0340]

(1) ethyl 3-[(4-nitrobenzoyl)amino]propanoate

To a mixture of 4-nitrobenzoic acid (16.7 g), β-alanine ethyl ester hydrochloride (18.4 g), 1-hydroxybenzotriazol·monohydrate (18.4 g), triethylamine (16.7 mL) and N,N-dimethylformamide (200 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (23.0 g), and the mixture was stirred at room temperature for 8 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with 1N hydrochloric acid and saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, and concentrated under reduced pressure to give a white solid.

Recrystallization from ethyl acetate-hexane gave the title object compound (26.6 g, 100%) as white crystals.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.29 (t, J=7.2 Hz, 3 H), 2.68 (t, J=6.1 Hz, 2 H), 3.76 (q, J=6.1 Hz, 2 H), 4.19 (q, J=7.1 Hz, 2H), 7.03 (br. s., 1 H), 7.93 (d, J=9.1 Hz, 2 H), 8.29 (d, J=8.7 Hz, 2 H).

[0341]

(2) ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate

A mixture of ethyl 3-[(4-nitrobenzoyl)amino]propanoate (26.6 g) synthesized above, 5% palladium-carbon (8.9 g), tetrahydrofuran (150 mL) and ethanol (150 mL) was stirred at room temperature overnight under a hydrogen atmosphere. 5% Palladium-carbon was filtered off, and the filtrate was concentrated under reduced pressure to give a white solid. Recrystallization from ethyl acetate-diisopropyl ether gave the title object compound (22.6 g, 95%) as white crystals.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.27 (t, J=7.2 Hz, 3H), 2.63 (t, J=6.0 Hz, 2 H), 3.70 (q, J=6.0 Hz, 2 H), 3.94 (br. s., 2 H), 4.17 (q, J=7.2 Hz, 2 H), 6.66 (d, J=8.7 Hz, 2 H), 7.60 (d, J=8.7 Hz, 2 H).

[0342]

(3) methyl 3-methyl-1H-pyrazole-4-carboxylate

A mixture of methyl acetoacetate (30.0 g) and dimethylformamide dimethylacetal (34.7 mL) was stirred at 100°C for 12 hr, and the mixture was allowed to cool. Ethanol (500 mL) and hydrazine monohydrate (12.6 mL) were added to the reaction mixture at room temperature, and the mixture was heated under reflux for 12 hr. The mixture was allowed to cool, and concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure to give the title object compound (22.3 g, 61%) as a pale-yellow solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.56 (s, 3H), 3.84 (s, 3H), 7.96 (s, 1H).

[0343]

(4) methyl 3-methyl-1-phenyl-1H-pyrazole-4-carboxylate

To a solution of methyl 3-methyl-1H-pyrazole-4-carboxylate (5.3 g) synthesized above in dimethylformamide (70 mL) was added sodium hydride (1.9 g, 60% in oil) at 0°C, and the mixture was stirred for 10 min. 2-Chloro-5-trifluoromethylpyridine (7.5 g) was added, and the mixture was stirred at room temperature overnight. Aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:10, volume ratio) to give the title object compound (3.3 g, 31%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.57 (s, 3 H), 3.87 (s, 3 H), 7.97 - 8.17 (m, 2 H), 8.63 - 8.74 (m, 1 H), 9.00 (s, 1 H).

[0344]

(5)3-methyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde

Methyl 3-methyl-1-phenyl-1H-pyrazole-4-carboxylate (3.3 g) synthesized above was dissolved in tetrahydrofuran (10 mL), and the solution was added dropwise to a solution (20 mL) of lithium aluminum hydride (0.45 g) in tetrahydrofuran at 0°C. The reaction mixture was stirred at 0°C for 30 min, and water (0.45 mL) was carefully added dropwise. Furthermore, 1N aqueous sodium hydroxide solution (2.3 mL) was added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was filtered through celite, and the residue was washed with tetrahydrofuran (30 mL). The extracts were combined, dried over magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in toluene (50 mL), manganese dioxide (8.8 g) was added, and the mixture was heated under reflux for 1 hr under dehydrating conditions. After allowing to cool, manganese dioxide was filtered off, and the residue was evaporated under reduced pressure to give

the title object compound (2.6 g, 87%) as a pale-yellow solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3 H), 7.97 - 8.17 (m, 2 H), 8.63 - 8.74 (m, 1 H), 9.00 (s, 1 H), 9.95 (s, 1 H).

[0345]

(6)cyclohexyl{3-methyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol

To a solution of 3-methyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde (2.6 g) synthesized above in tetrahydrofuran (40 mL) was added dropwise 1M cyclohexylmagnesium bromide tetrahydrofuran solution (15 mL) at 0°C. After stirring at 0°C for 1 hr, aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (2.0 g, 36%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.93 (m, 11 H), 2.36 (s, 3 H), 3.62 (br. s., 1 H), 4.44 (dd, J=7.2, 3.4 Hz, 1 H), 7.91 - 8.07 (m, 2 H), 8.43 (s, 1 H), 8.63 (s, 1 H).

[0346]

(7)3-[({4-[(cyclohexyl{3-methyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

To a solution (10 mL) of cyclohexyl{3-methyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.75 g) synthesized above in tetrahydrofuran was added thionyl chloride (0.24 mL) at room temperature, and the mixture was stirred for 30 min. The reaction mixture was poured into aqueous sodium hydrogen carbonate solution at 0°C, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (15 mL), and sodium iodide (0.63 g), sodium carbonate (0.45 g) and ethyl 3-{[(4-

aminophenyl)carbonyl]amino}propanoate (0.75 g) synthesized in Example 1, (2) were added. The mixture was stirred at 80°C overnight and allowed to cool. Then, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound in an ethyl ester form (876 mg). This was dissolved in ethanol (4 mL), 1N aqueous sodium hydroxide solution (4 mL) was added at room temperature, and the mixture was stirred for 1 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (4 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.78 g, 70%) as a white solid.

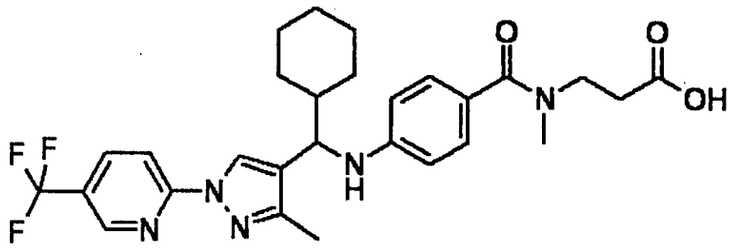
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.81 - 2.23 (m, 11 H), 2.34 (s, 3 H), 2.50 - 2.68 (m, 2 H), 3.43 - 3.74 (m, 2 H), 4.20 (d, J=6.4 Hz, 1 H), 6.47 (d, J=8.5 Hz, 2 H), 6.68 (br. s., 1 H), 7.51 (d, J=8.5 Hz, 2 H), 7.86 - 8.05 (m, 2 H), 8.31 (s, 1 H), 8.57 (s, 1 H).

[0347]

Example 2

3-[({4-[(cyclohexyl{3-methyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0348]



[0349]

(1) ethyl 3-[methyl(4-nitrobenzoyl)amino]propanoate

Using ethyl 3-(methylamino)propanoate (13.1 g) and in the same manner as in Example 1(1), the title object compound

(28.0 g, 100%) was obtained as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.26 (t, J=7.1 Hz, 3 H), 2.51-2.78 (m, 2 H), 2.99-3.10 (m, 3H), 3.46-3.86 (m, 2 H), 4.03-4.28 (m, 2 H), 7.50-7.65 (m, 2 H), 8.28 (d, J=8.7 Hz, 2 H).

[0350]

(2) ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate

In the same manner as in Example 1(2), the title object compound (26.6 g, 90%) was obtained as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.26 (t, J=7.2 Hz, 3 H), 2.64 (t, J=6.4 Hz, 2 H), 3.05 (s, 3 H), 3.74 (t, J=7.0 Hz, 2 H), 3.85 (br. s., 2 H), 4.14 (q, J=7.2 Hz, 2 H), 6.59-6.72 (m, 2 H), 7.23-7.28 (m, 2 H).

[0351]

(3) 3-[({4-[(cyclohexyl{3-methyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

Using cyclohexyl{3-methyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.75 g) synthesized in Example 1(6) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.80 g) synthesized in Example 2(2) and in the same manner as in Example 1 (7), the title object compound (0.74 g, 65%) was obtained as a white solid.

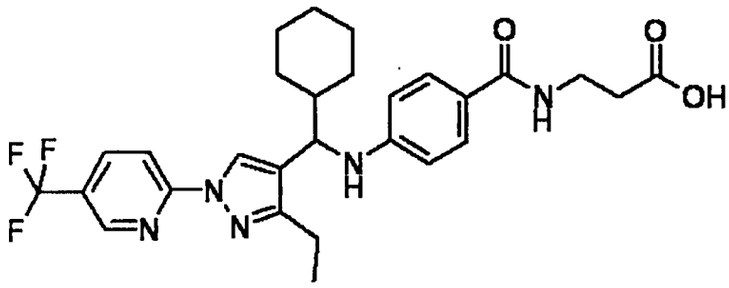
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 2.23 (m, 11 H), 2.37 (s, 3 H), 2.62 - 2.78 (m, 2 H), 3.05 (s, 3 H), 3.58 - 3.84 (m, 2 H), 4.21 (d, J=6.1 Hz, 1 H), 6.49 (d, J=8.7 Hz, 2 H), 7.24 (d, J=8.7 Hz, 2 H), 7.90 - 8.00 (m, 2 H), 8.32 (s, 1 H), 8.59 (s, 1 H).

[0352]

Example 3

3-[({4-[(cyclohexyl{3-ethyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[0353]



[0354]

(1) methyl 3-ethyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate

A mixture of methyl 3-oxopentanoate (2.6 g) and dimethylformamide dimethylacetal (2.8 mL) was stirred at 100°C for 12 hr, and allowed to cool. Ethanol (50 mL) and hydrazine monohydrate (1.1 mL) were added to the reaction mixture, and the mixture was treated in the same manner as in Example 1(3) to give a crude product of methyl 3-ethyl-1H-pyrazole-4-carboxylate. This was dissolved in dimethylformamide (30 ml), potassium carbonate (4.2 g) and 2-chloro-5-trifluoromethylpyridine (3.6 g) were added, and the mixture was stirred at 100°C for 2 hr. In the same manner as in Example 1(4), the title object compound (4.7 g, 79%) was obtained as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.33 (t, J=7.5 Hz, 3 H), 3.00 (q, J=7.5 Hz, 2 H), 3.87 (s, 3 H), 7.99 - 8.18 (m, 2 H), 8.68 (s, 1 H), 9.00 (s, 1 H).

[0355]

(2) 3-ethyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde

Methyl 3-ethyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate (4.7 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (1.1 g, 26%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.35 (t, J=7.6 Hz, 3 H), 3.00 (q, J=7.6 Hz, 2 H), 7.98 - 8.23 (m, 2 H), 8.71 (s, 1 H), 9.04 (s, 1 H), 10.05 (s, 1 H).

[0356]

(3) cyclohexyl{3-ethyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol

3-Ethyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde (1.1 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (1.1 g, 79%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.80 - 2.21 (m, 14 H), 2.73 (q, J=7.3 Hz, 2 H), 4.44 (dd, J=7.2, 3.4 Hz, 1 H), 7.87 - 8.16 (m, 2 H), 8.43 (s, 1 H), 8.63 (s, 1 H).

[0357]

(4) 3-[({4-[(cyclohexyl{3-ethyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

Using cyclohexyl{3-ethyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.55 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.37 g) synthesized in Example 1(2) and in the same manner as in Example 1 (7), the title object compound (0.32 g, 38%) was obtained as a white solid.

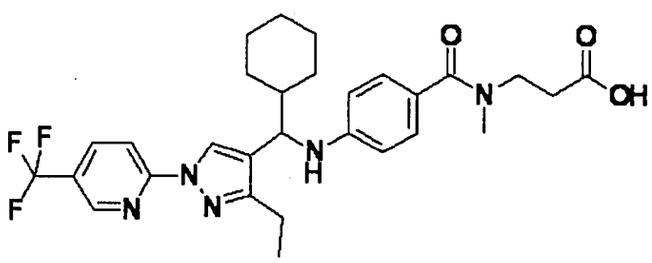
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 - 2.00 (m, 11 H), 1.32 (t, J=7.5 Hz, 3 H), 2.38 - 2.58 (m, 2 H), 2.70 (q, J=7.5 Hz, 2 H), 3.39 - 3.69 (m, 2 H), 4.22 (d, J=6.0 Hz, 1 H), 6.47 (d, J=8.5 Hz, 2 H), 6.68 (br. s., 1 H), 7.51 (d, J=8.5 Hz, 2 H), 7.85 - 8.08 (m, 2 H), 8.30 (s, 1 H), 8.56 (s, 1 H).

[0358]

Example 4

3-[({4-[(cyclohexyl{3-ethyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0359]



[0360]

Using cyclohexyl{3-ethyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.55 g) synthesized in Example 3(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.39 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.35 g, 41%) was obtained as a white solid.

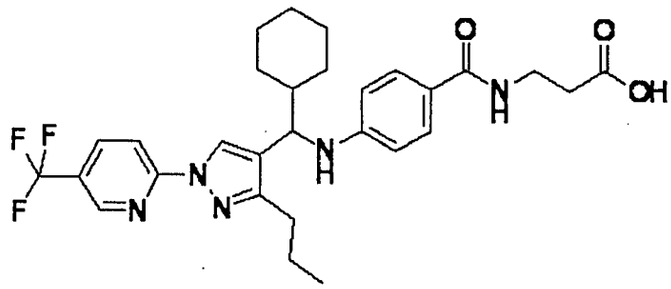
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.19 - 2.06 (m, 11 H), 1.35 (t, J=7.5 Hz, 3 H), 2.60 - 2.81 (m, 4 H), 3.05 (s, 3 H), 3.72 (d, J=7.5 Hz, 1 H), 4.24 (d, J=6.2 Hz, 1 H), 6.50 (d, J=8.7 Hz, 2 H), 7.26 (d, J=8.7 Hz, 2 H), 7.91 - 8.09 (m, 2 H), 8.31 (s, 1 H), 8.59 (s, 1 H).

[0361]

Example 5

3-[({4-[(cyclohexyl{3-propyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[0362]



[0363]

(1) methyl 3-propyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate

A mixture of methyl 3-oxohexanoate (2.1 g) and dimethylformamide dimethylacetal (2.1 mL) was stirred at 100°C for 12 hr, and the mixture was allowed to cool. To the reaction mixture were added ethanol (50 mL) and hydrazine monohydrate (0.75 mL). In the same manner as in Example 1(3), a crude product of methyl 3-propyl-1H-pyrazole-4-carboxylate was obtained. This was dissolved in dimethylformamide (20 ml),

potassium carbonate (3.0 g) and 2-chloro-5-trifluoromethylpyridine (2.7 g) were added, and the mixture was stirred at 100°C for 2 hr. In the same manner as in Example 1(4), the title object compound (3.3 g, 71%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 (t, J=7.4 Hz, 3 H), 1.69 - 1.88 (m, 2 H), 2.93 (d, J=7.7 Hz, 2 H), 3.87 (s, 3 H), 7.98 - 8.19 (m, 2 H), 8.69 (s, 1 H), 9.00 (s, 1 H).

[0364]

(2) 3-propyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde

Methyl 3-propyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate (3.3 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (1.1 g, 35%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 (t, J=7.3 Hz, 3 H), 1.79 (m, 2 H), 2.94 (d, J=7.7 Hz, 2 H), 8.00 - 8.23 (m, 2 H), 8.71 (s, 1 H), 9.04 (s, 1 H), 10.05 (s, 1 H).

[0365]

(3) cyclohexyl{3-propyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol

3-Propyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde (1.1 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (1.3 g, 95%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.80 - 2.21 (m, 16 H), 2.67 (q, J=7.8 Hz, 2 H), 4.44 (dd, J=7.5, 3.4 Hz, 1 H), 7.90 - 8.16 (m, 2 H), 8.43 (s, 1 H), 8.63 (s, 1 H).

[0366]

(4) 3-[({4-[(cyclohexyl{3-propyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

Using cyclohexyl{3-propyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.65 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.42 g)

synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.38 g, 39%) was obtained as a white solid.

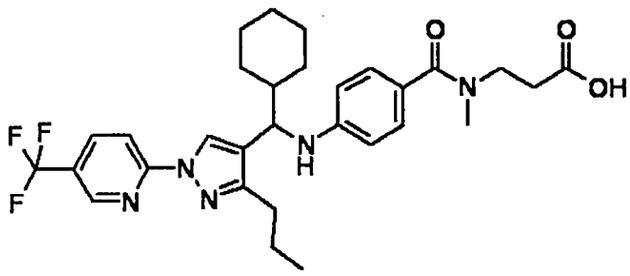
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 (t, J=7.4 Hz, 3 H), 1.07 - 2.04 (m, 13 H), 2.49 - 2.74 (m, 4 H), 3.52 - 3.72 (m, 2 H), 4.24 (d, J=6.4 Hz, 1 H), 6.50 (d, J=8.7 Hz, 2 H), 6.55 - 6.68 (m, 1 H), 7.53 (d, J=8.7 Hz, 2 H), 7.86 - 8.08 (m, 2 H), 8.31 (s, 1 H), 8.57 (s, 1 H).

[0367]

Example 6

3-[({4-[(cyclohexyl{3-propyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0368]



[0369]

Using cyclohexyl{3-propyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.65 g) synthesized in Example 5(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.44 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.34 g, 34%) was obtained as a white solid.

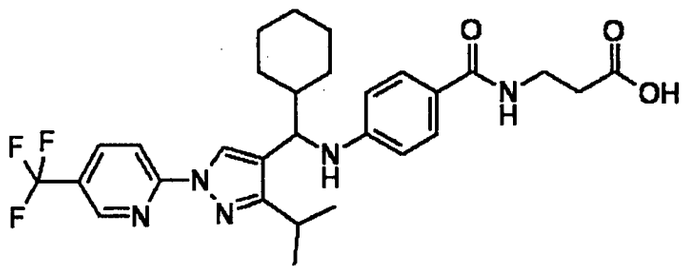
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 (t, J=7.2 Hz, 3 H), 1.08 - 2.13 (m, 13 H), 2.54 - 2.78 (m, 4 H), 3.05 (s, 3 H), 3.71 (t, J=6.2 Hz, 1 H), 4.24 (d, J=5.7 Hz, 1 H), 6.50 (d, J=8.7 Hz, 2 H), 7.26 (d, J=8.7 Hz, 2 H), 7.87 - 8.12 (m, 2 H), 8.31 (s, 1 H), 8.59 (s, 1 H).

[0370]

Example 7

3-[({4-[(cyclohexyl{3-(1-methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[0371]



[0372]

(1) methyl 3-(1-methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate

Using methyl 4-methyl-3-oxopentanoate (2.9 g), dimethylformamide dimethylacetal (2.8 mL) and hydrazine monohydrate (1.1 mL) and in the same manner as in Example 1(3), a crude product of methyl 3-(1-methylethyl)-1H-pyrazole-4-carboxylate was obtained. This was dissolved in dimethylformamide (30 ml), potassium carbonate (4.2 g) and 2-chloro-5-trifluoromethylpyridine (3.6 g) were added, and the mixture was stirred at 100°C for 2 hr. In the same manner as in an Example 1(4), the title object compound (4.6 g, 73%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.36 (d, J=6.8 Hz, 6 H), 3.60 (quint, J=6.8 Hz, 1 H), 3.87 (s, 3 H), 7.99 - 8.99 (m, 4 H).

[0373]

(2) 3-(1-methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde

Methyl 3-(1-methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate (4.6 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (1.7 g, 40%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.38 (d, J=6.8 Hz, 6 H), 3.41 - 3.64 (m, 1 H), 8.01 - 8.28 (m, 2 H), 8.70 (s, 1 H), 9.04 (s, 1 H), 10.06 (s, 1 H).

[0374]

(3)cyclohexyl{3-(1-methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol

3-(1-Methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde (1.7 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (1.5 g, 71%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.80 - 2.21 (m, 17 H), 3.01 (quint, J=6.9 Hz, 1 H), 4.45 (dd, J=7.5, 3.6 Hz, 1 H), 7.90 - 8.10 (m, 2 H), 8.43 (s, 1 H), 8.62 (s, 1 H).

[0375]

(4)3-[({4-[(cyclohexyl{3-(1-methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

Using cyclohexyl{3-(1-methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.50 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.32 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.11 g, 14%) was obtained as a pale-yellow solid.

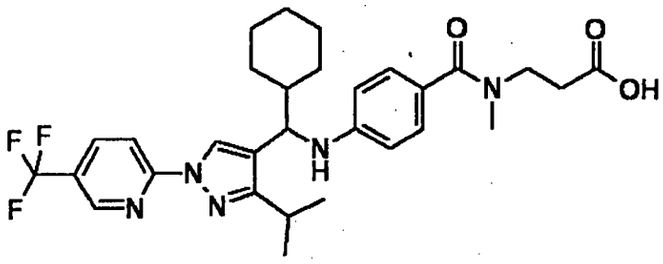
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.20 - 2.06 (m, 11 H), 1.28 - 1.40 (m, 6 H), 2.64 (t, J=4.5 Hz, 2 H), 2.91 - 3.17 (m, 1 H), 3.54 - 3.79 (m, 2 H), 4.29 (d, J=6.2 Hz, 1 H), 6.43 - 6.65 (m, 3 H), 7.54 (d, J=8.7 Hz, 2 H), 7.86 - 8.11 (m, 2 H), 8.30 (s, 1 H), 8.58 (s, 1 H).

[0376]

Example 8

3-[({4-[(cyclohexyl{3-(1-methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0377]



[0378]

Using cyclohexyl{3-(1-methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.65 g) synthesized in Example 7(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.34 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.16 g, 21%) was obtained as a white solid.

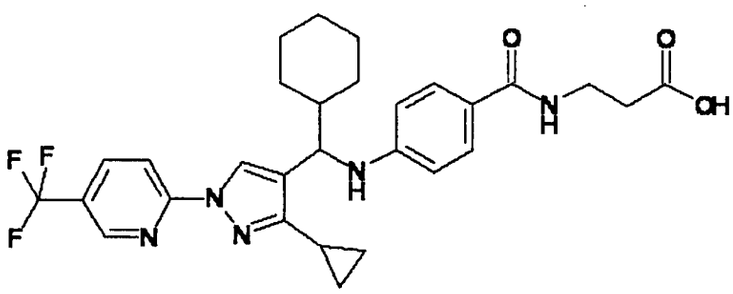
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.20 - 2.05 (m, 11 H), 1.32 - 1.37 (m, 6 H), 2.59 - 2.79 (m, 2 H), 2.96 - 3.20 (m, 4 H), 3.73 (t, J=7.5 Hz, 2 H), 4.28 (d, J=6.0 Hz, 1 H), 6.52 (d, J=8.7 Hz, 2 H), 7.26 (d, J=8.7 Hz, 2 H), 7.88 - 8.11 (m, 2 H), 8.30 (s, 1 H), 8.59 (s, 1 H).

[0379]

Example 9

3-[({4-[(cyclohexyl{3-cyclopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[0380]



[0381]

(1) methyl 3-cyclopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate

Using methyl 3-cyclopropyl-3-oxopropanoate (2.8 g), dimethylformamide dimethylacetal (2.8 mL) and hydrazine

monohydrate (1.1 mL) and in the same manner as in Example 1(3), a crude product of methyl 3-cyclopropyl-1H-pyrazole-4-carboxylate was obtained. This was dissolved in dimethylformamide (30 ml), potassium carbonate (4.2 g) and 2-chloro-5-trifluoromethylpyridine (3.6 g) were added, and the mixture was stirred at 100°C for 2 hr. In the same manner as in Example 1(4), the title object compound (4.8 g, 77%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.10 (m, 4 H), 2.55 - 2.70 (m, 1 H), 3.89 (s, 3 H), 8.00 - 8.03 (m, 2 H), 8.66 (s, 1 H), 8.96 (s, 1 H).

[0382]

(2) 3-cyclopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde

Methyl 3-cyclopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate (4.8 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (1.5 g, 36%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.15 (m, 4 H), 2.50 - 2.70 (m, 1 H), 8.00 - 8.10 (m, 2 H), 8.69 (s, 1 H), 8.99 (s, 1 H), 10.10 (s, 1 H).

[0383]

(3) cyclohexyl{3-cyclopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol

3-Cyclopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde (1.5 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (2.1 g, 99%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.80 - 2.10 (m, 16 H), 4.48 (dd, J=7.3, 3.0 Hz, 1 H), 7.90 - 8.10 (m, 2 H), 8.40 (s, 1 H), 8.60 (s, 1 H).

[0384]

(4) 3-[({4-[(cyclohexyl{3-cyclopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

Using cyclohexyl{3-cyclopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.50 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.32 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.15 g, 21%) was obtained as a white solid.

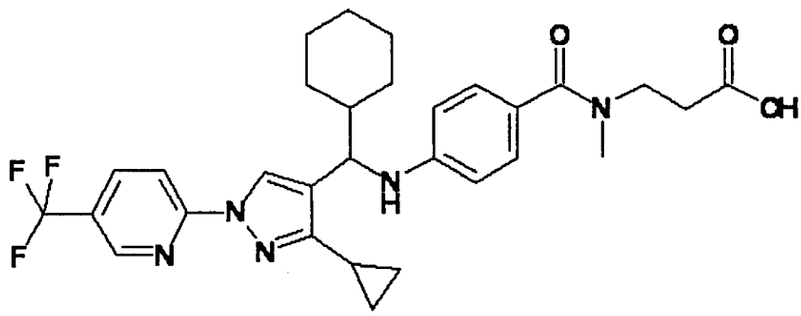
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 - 2.07 (m, 16 H), 2.64 (t, J=5.5 Hz, 2 H), 3.65 (q, J=5.9 Hz, 2 H), 4.37 (d, J=6.4 Hz, 1 H), 6.54 - 6.70 (m, 3 H), 7.53 (d, J=8.3 Hz, 2 H), 7.93 (s, 2 H), 8.28 (s, 1 H), 8.56 (s, 1 H).

[0385]

Example 10

3-[({4-[(cyclohexyl{3-cyclopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0386]



[0387]

Using cyclohexyl{3-cyclopropyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.50 g) synthesized in Example 9(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.34 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.19 g, 25%) was obtained as a white solid.

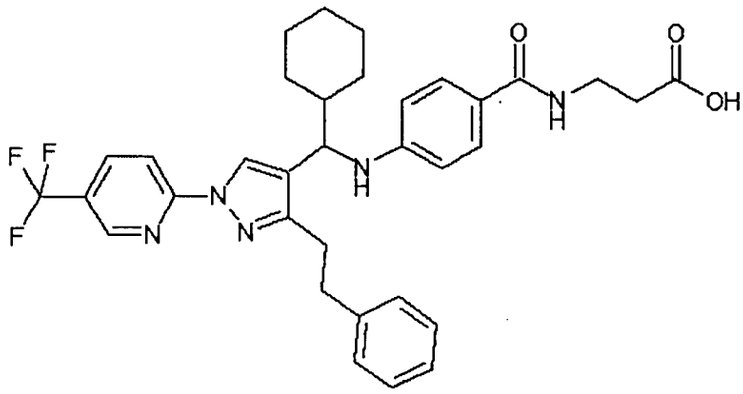
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 2.09 (m, 16 H), 2.71 (t, J=6.2 Hz, 2 H), 3.07 (s, 3 H), 3.71 (t, J=6.4 Hz, 2 H), 4.36 (d, J=6.4 Hz, 1 H), 6.54 (d, J=8.7 Hz, 2 H), 7.26 (d, J=8.7 Hz, 2 H), 7.94 (s, 2 H), 8.28 (s, 1 H), 8.57 (s, 1 H).

[0388]

Example 11

3-[({4-[(cyclohexyl{3-(2-phenylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[0389]



[0390]

(1) ethyl 3-(2-phenylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate

Using ethyl 3-oxo-5-phenylpentanoate (5.8 g), dimethylformamide dimethylacetal (3.6 mL) and hydrazine monohydrate (1.3 mL) and in the same manner as in Example 1(3), a crude product of ethyl 3-(2-phenylethyl)-1H-pyrazole-4-carboxylate was obtained. This was dissolved in dimethylformamide (30 ml), potassium carbonate (5.5 g) and 2-chloro-5-trifluoromethylpyridine (4.8 g) were added, and the mixture was stirred at 100°C overnight. In the same manner as in Example 1(4), the title object compound (5.2 g, 50%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.39 (t, J=7.2 Hz, 3 H), 3.00 - 3.15 (m, 2 H), 3.22 - 3.39 (m, 2 H), 4.34 (q, J=7.2 Hz, 2 H), 7.15 - 7.38 (m, 10 H), 7.99 - 8.17 (m, 2 H), 8.69 (s, 1 H), 9.01 (s, 1 H).

[0391]

(2) 3-(2-phenylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde

Ethyl 3-(2-phenylethyl)-1-[5-(trifluoromethyl)pyridin-2-

yl]-1H-pyrazole-4-carboxylate (5.2 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (3.0 g, 65%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.98 - 3.17 (m, 2 H), 3.22 - 3.41 (m, 2 H), 7.11 - 7.47 (m, 5 H), 7.99 - 8.22 (m, 2 H), 8.71 (s, 1 H), 9.04 (s, 1 H), 9.99 (s, 1 H).

[0392]

(3) cyclohexyl{3-(2-phenylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol

3-(2-Phenylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde (1.5 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (1.7 g, 95%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.83 - 2.02 (m, 12 H), 2.92 - 3.23 (m, 4 H), 4.28 (dd, J=7.3, 2.7 Hz, 1 H), 7.15 - 7.40 (m, 5 H), 7.93 - 8.13 (m, 2 H), 8.42 (s, 1 H), 8.64 (s, 1 H).

[0393]

(4) 3-[({4-[(cyclohexyl{3-(2-phenylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

Using cyclohexyl{3-(2-phenylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.50 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.28 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.20 g, 28%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 - 1.97 (m, 11 H), 2.45 - 2.64 (m, 2 H), 2.87 - 3.18 (m, 4 H), 3.49 - 3.67 (m, 2 H), 4.16 (d, J=6.0 Hz, 1 H), 6.41 (d, J=8.7 Hz, 2 H), 6.61 (br. s., 1 H), 7.15 - 7.34 (m, 5 H), 7.49 (d, J=8.7 Hz, 2 H), 7.87 - 8.10 (m, 2 H), 8.31 (s, 1 H), 8.57 (s, 1 H).

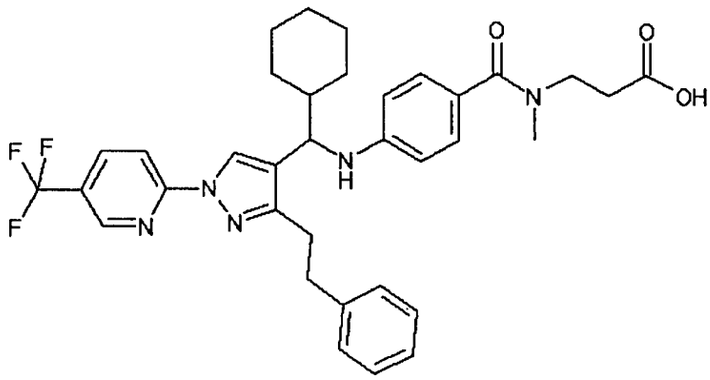
[0394]

Example 12

3-[({4-[(cyclohexyl{3-(2-phenylethyl)-1-[5-

(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0395]



[0396]

Using cyclohexyl{3-(2-phenylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.50 g) synthesized in Example 11(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.35 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.30 g, 41%) was obtained as a white solid.

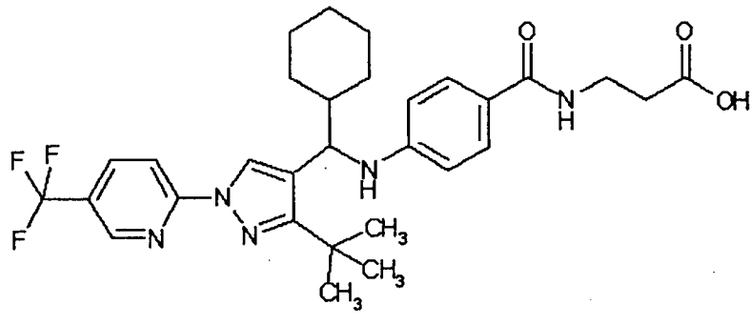
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 2.01 (m, 11 H), 2.59 - 2.74 (m, 2 H), 2.89 - 3.20 (m, 7 H), 3.71 (d, J=6.0 Hz, 2 H), 4.18 (d, J=6.0 Hz, 1 H), 6.43 (d, J=8.7 Hz, 2 H), 7.16 - 7.37 (m, 5 H), 7.90 - 8.13 (m, 2 H), 8.32 (s, 1 H), 8.60 (s, 1 H).

[0397]

Example 13

3-{[(4-{[{3-tert-butyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0398]



[0399]

(1) methyl 3-tert-butyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate

Using ethyl 4,4-dimethyl-3-oxopentanoate (3.4 g), dimethylformamide dimethylacetal (2.8 mL) and hydrazine monohydrate (1.1 mL), and in the same manner as in Example 1(3), a crude product of methyl 3-tert-butyl-1H-pyrazole-4-carboxylate was obtained. This was dissolved in dimethylformamide (15 ml), potassium carbonate (1.2 g) and 2-chloro-5-trifluoromethylpyridine (1.7 g) were added, and the mixture was stirred at room temperature overnight. In the same manner as in Example 1(4), the title object compound (2.8 g, 43%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.38 (t, J=7.2 Hz, 3 H), 1.49 (s, 9 H), 4.32 (q, J=7.2 Hz, 2 H), 7.98 - 8.21 (m, 2 H), 8.68 (d, J=1.1 Hz, 1 H), 9.03 (s, 1 H).

[0400]

(2) 3-tert-butyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde

Methyl 3-tert-butyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate (2.8 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (1.7 g, 93%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.49 (s, 9 H), 7.98 - 8.21 (m, 2 H), 8.68 (d, J=1.1 Hz, 1 H), 9.09 (s, 1 H), 10.11 (s, 1 H).

[0401]

(3) cyclohexyl{3-tert-butyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol

3-Tert-butyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-

pyrazole-4-carbaldehyde (1.7 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (1.1 g, 49%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.79 - 2.20 (m, 12 H), 1.43 (s, 9 H), 4.65 (d, J=9.0 Hz, 1 H), 7.91 - 8.15 (m, 2 H), 8.52 (s, 1 H), 8.62 (s, 1 H).

[0402]

(4) 3-{[(4-{[{3-tert-butyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

Using cyclohexyl{3-tert-butyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.53 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.32 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.12 g, 15%) was obtained as a white solid.

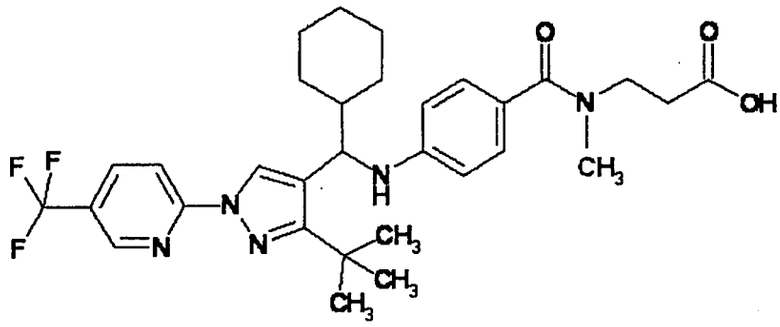
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 2.00 (m, 11 H), 1.27 (s, 9 H), 2.57 - 2.61 (m, 2 H), 3.17 - 3.59 (m, 2 H), 4.44 (br. s., 1 H), 6.31 - 6.51 (m, 2 H), 7.33 - 7.47 (m, 1 H), 7.49 - 7.62 (m, 2 H), 7.74 - 8.07 (m, 2 H), 8.32 - 8.57 (m, 2 H).

[0403]

Example 14

3-{[(4-{[{3-tert-butyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[0404]



[0405]

Using cyclohexyl{3-tert-butyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.52 g) synthesized in Example 13(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.34 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.13 g, 16%) was obtained as a white solid.

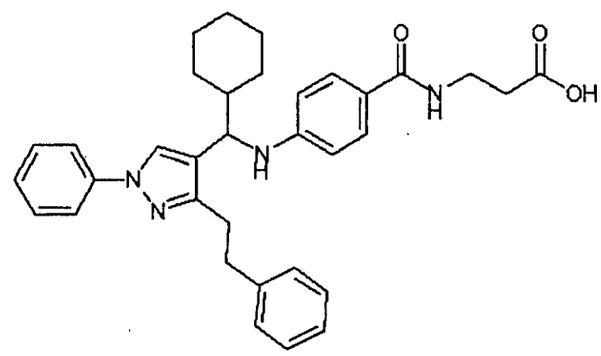
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 2.00 (m, 11 H), 1.42 (s, 9 H), 2.61 - 2.81 (m, 2 H), 3.08 (s, 3 H), 3.72 (t, J=6.4 Hz, 2 H), 4.57 (d, J=6.1 Hz, 1 H), 6.54 (d, J=8.7 Hz, 2 H), 7.26 (d, J=8.7 Hz, 2 H), 7.89 - 8.13 (m, 2 H), 8.40 (s, 1 H), 8.59 (s, 1 H).

[0406]

Example 15

3-({[4-({cyclohexyl[1-phenyl-3-(2-phenylethyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0407]



[0408]

(1) ethyl 1-phenyl-3-(2-phenylethyl)-1H-pyrazole-4-carboxylate

A mixture of ethyl 3-oxo-5-phenylpentanoate (5.8 g) and

dimethylformamide dimethylacetal (3.6 mL) was stirred at 100°C overnight, and the mixture was allowed to cool to room temperature. To the reaction mixture were added ethanol (30 mL) and phenylhydrazine (2.9 g), and the mixture was further stirred at 100°C for 8 hr. After allowing to cool, ethanol was evaporated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:10, volume ratio) to give the title object compound (7.1 g, 84%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.40 (t, J=7.2 Hz, 3 H), 2.87 (dd, J=9.0, 6.6 Hz, 2 H), 3.15 - 3.32 (m, 2 H), 4.36 (q, J=7.2 Hz, 2 H), 6.92 - 7.53 (m, J=7.5, 3.8, 3.8, 3.5 Hz, 10 H), 8.05 (s, 1 H).

[0409]

(2) 1-phenyl-3-(2-phenylethyl)-1H-pyrazole-4-carbaldehyde

Ethyl 1-phenyl-3-(2-phenylethyl)-1H-pyrazole-4-carboxylate (7.1 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (4.6 g, 75%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.87 (t, J=7.8 Hz, 2 H), 3.23 (t, J=7.6 Hz, 2 H), 6.84 - 7.58 (m, 10 H), 8.07 (s, 1 H), 9.93 (s, 1 H).

[0410]

(3) cyclohexyl[1-phenyl-3-(2-phenylethyl)-1H-pyrazol-4-yl]methanol

1-Phenyl-3-(2-phenylethyl)-1H-pyrazole-4-carbaldehyde (2.6 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (2.9 g, 85%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.75 - 2.19 (m, 12 H), 2.46 - 3.17 (m, 4 H), 4.16 (dd, J=8.3, 2.7 Hz, 1 H), 6.83 - 7.54 (m, 10 H), 7.58 (s, 1 H).

[0411]

(4) 3-({[4-({cyclohexyl[1-phenyl-3-(2-phenylethyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

Using cyclohexyl[1-phenyl-3-(2-phenylethyl)-1H-pyrazol-4-yl]methanol (0.50 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.33 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.31 g, 41%) was obtained as a white solid.

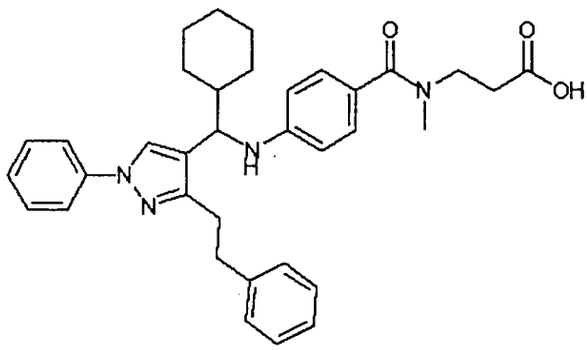
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 2.03 (m, 11 H), 2.40 - 2.56 (m, 2 H), 2.67 (t, J=5.7 Hz, 2 H), 2.91 - 3.07 (m, 2 H), 3.68 (q, J=5.9 Hz, 2 H), 4.20 (d, J=7.0 Hz, 1 H), 6.52 - 6.58 (m, J=8.7 Hz, 3 H), 6.82 (d, J=8.6 Hz, 2 H), 7.12 - 7.22 (m, 4 H), 7.35 - 7.65 (m, 11 H).

[0412]

Example 16

3-[{[4-({cyclohexyl[1-phenyl-3-(2-phenylethyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0413]



[0414]

Using cyclohexyl[1-phenyl-3-(2-phenylethyl)-1H-pyrazol-4-yl]methanol (0.50 g) synthesized in Example 15(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.35 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.37 g, 47%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 2.08 (m, 11 H), 2.44 -

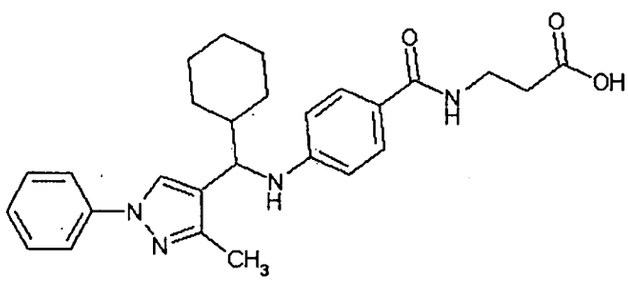
2.59 (m, 2 H), 2.73 (d, J=6.0 Hz, 2 H), 2.91 - 3.05 (m, 2 H), 3.09 (s, 3 H), 3.73 (t, J=6.4 Hz, 2 H), 4.19 (d, J=6.8 Hz, 1 H), 6.53 (d, J=8.7 Hz, 2 H), 6.79 - 6.88 (m, 2 H), 7.12 - 7.58 (m, 11 H).

[0415]

Example 17

3-{[(4-{[cyclohexyl(3-methyl-1-phenyl-1H-pyrazol-4-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0416]



[0417]

(1) methyl 3-methyl-1-phenyl-1H-pyrazole-4-carboxylate

Methyl 3-methyl-1H-pyrazole-4-carboxylate (14.4 g) synthesized in Example 1, (3) was dissolved in dimethylacetamide (200 mL), phenylboronic acid (25.0 g), copper acetate (36.4 g) and pyridine (32 mL) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, 1N hydrochloric acid (100 mL) was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=10:1, volume ratio) to give the title object compound (11.4 g, 53%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.56 (s, 3H), 3.86 (s, 3H), 7.26-7.70 (m, 5H), 8.34 (s, 1H).

[0418]

(2) 3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde

Methyl 3-methyl-1-phenyl-1H-pyrazole-4-carboxylate (11.4 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (3.8 g, 39%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.59 (s, 3H), 7.27-7.72 (m, 5H), 8.34 (s, 1H), 10.00 (s, 1H).

[0419]

(3) cyclohexyl(3-methyl-1-phenyl-1H-pyrazol-4-yl)methanol

3-Methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (3.8 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (4.4 g, 79%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.80-2.20 (m, 11H), 2.34 (s, 3H), 3.61 (br s, 1H), 4.44 (d, J=7.2 Hz, 1H), 7.20-7.80 (m, 6H).

[0420]

(4) 3-{[(4-{[cyclohexyl(3-methyl-1-phenyl-1H-pyrazol-4-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

Using cyclohexyl(3-methyl-1-phenyl-1H-pyrazol-4-yl)methanol (0.14 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.15 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.05 g, 31%) was obtained as a white solid.

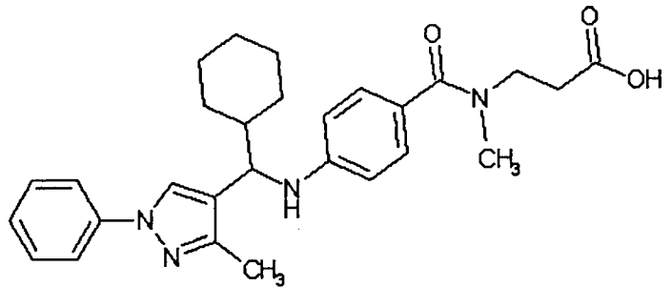
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 - 2.21 (m, 12 H), 2.36 (s, 3 H), 2.65 (br. s., 2 H), 3.67 (br. s., 2 H), 4.20 (d, J=6.0 Hz, 1 H), 6.49 (d, J=6.0 Hz, 2 H), 6.55 - 6.71 (m, 1 H), 7.14 - 7.74 (m, 8 H).

[0421]

Example 18

3-{[(4-{[cyclohexyl(3-methyl-1-phenyl-1H-pyrazol-4-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0422]



[0423]

Using cyclohexyl(3-methyl-1-phenyl-1H-pyrazol-4-yl)methanol (0.14 g) synthesized in Example 17(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.15 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.04 g, 23%) was obtained as a white solid.

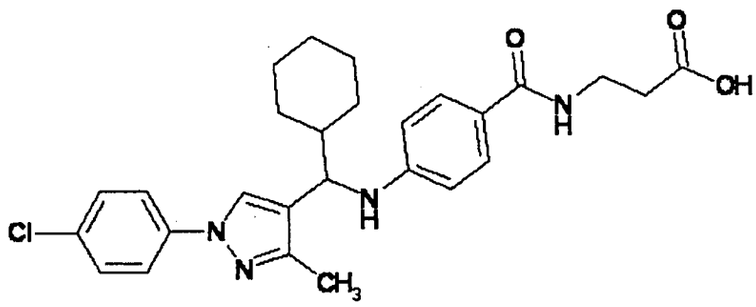
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.87 - 2.10 (m, 12 H), 2.25 (s, 3 H), 2.47 (t, J=7.4 Hz, 2 H), 2.89 (s, 3 H), 3.51 (t, J=7.4 Hz, 2 H), 4.16 (t, J=7.6 Hz, 1 H), 6.22 (d, J=8.0 Hz, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 7.10 (d, J=8.7 Hz, 2 H), 7.22 (t, J=7.2 Hz, 1 H), 7.43 (t, J=8.0 Hz, 1 H).

[0424]

Example 19

3-({[4-({[1-(4-chlorophenyl)-3-methyl-1H-pyrazol-4-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0425]



[0426]

(1) methyl 1-(4-chlorophenyl)-3-methyl-1H-pyrazole-4-carboxylate

(87)

Using methyl 3-methyl-1H-pyrazole-4-carboxylate (6.25 g) synthesized in Example 1(3), 4-chlorophenylboronic acid (13.9 g), copper acetate (16.3 g) and pyridine (14.4 mL), and in the same manner as in Example 17(1), the title object compound (6.9 g, 62%) was obtained as a white solid.

$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 2.54 (s, 3 H), 3.85 (s, 3 H), 7.43 (d, J=8.7 Hz, 2 H), 7.62 (d, J=8.7 Hz, 2 H), 8.31 (s, 1 H).

[0427]

(2) 1-(4-chlorophenyl)-3-methyl-1H-pyrazole-4-carbaldehyde

Methyl 1-(4-chlorophenyl)-3-methyl-1H-pyrazole-4-carboxylate (6.9 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (4.1 g, 68%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.58 (s, 3 H), 7.46 (d, J=9.0 Hz, 2 H), 7.64 (d, J=9.0 Hz, 2 H), 8.31 (s, 1 H), 10.00 (s, 1 H).

[0428]

(3) [1-(4-chlorophenyl)-3-methyl-1H-pyrazol-4-yl](cyclohexyl)methanol

1-(4-Chlorophenyl)-3-methyl-1H-pyrazole-4-carbaldehyde (4.2 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (4.9 g, 85%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.88 - 2.00 (m, 11 H), 2.32 (s, 3 H), 3.59 (br. s., 1 H), 4.43 (d, J=7.2 Hz, 1 H), 7.38 (d, J=9.0 Hz, 2 H), 7.58 (d, J=9.0 Hz, 2 H), 7.76 (s, 1 H).

[0429]

(4) 3-({[4-({[1-(4-chlorophenyl)-3-methyl-1H-pyrazol-4-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}amino)propanoic acid

Using [1-(4-chlorophenyl)-3-methyl-1H-pyrazol-4-yl](cyclohexyl)methanol (0.46 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.35 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.42 g, 57%) was

obtained as a white solid.

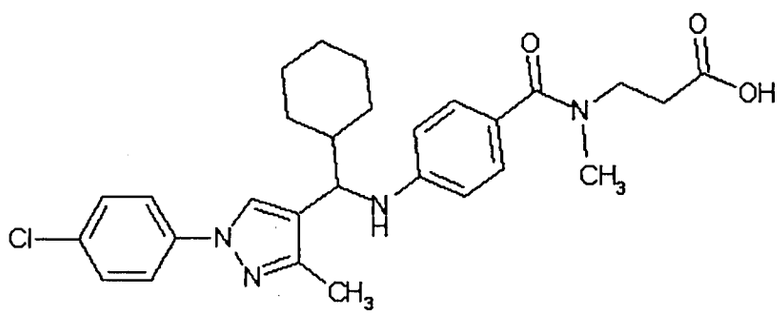
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.86 - 2.09 (m, 12 H), 2.24 (s, 3 H), 2.41 (t, J=7.1 Hz, 2 H), 3.28 - 3.44 (m, 2 H), 4.20 (t, J=7.7 Hz, 1 H), 6.33 (d, J=7.9 Hz, 1 H), 6.58 (d, J=8.9 Hz, 2 H), 7.39 - 7.60 (m, 4 H), 7.73 (d, J=9.0 Hz, 2 H), 7.92 - 8.09 (m, 1 H), 8.29 (s, 1 H).

[0430]

Example 20

3-[{[4-({[1-(4-chlorophenyl)-3-methyl-1H-pyrazol-4-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoic acid

[0431]



[0432]

Using [1-(4-chlorophenyl)-3-methyl-1H-pyrazol-4-yl](cyclohexyl)methanol (0.46 g) synthesized in Example 19(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.25 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.41 g, 57%) was obtained as a white solid.

$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.75 - 2.07 (m, 12 H), 2.23 (s, 5 H), 2.85 (br. s., 3 H), 3.39 - 3.57 (m, 2 H), 4.13 (br. s., 1 H), 6.20 (d, J=7.0 Hz, 1 H), 6.56 (d, J=8.5 Hz, 2 H), 7.09 (d, J=8.5 Hz, 2 H), 7.46 (d, J=8.7 Hz, 2 H), 7.71 (d, J=8.7 Hz, 2 H), 8.28 (s, 1 H).

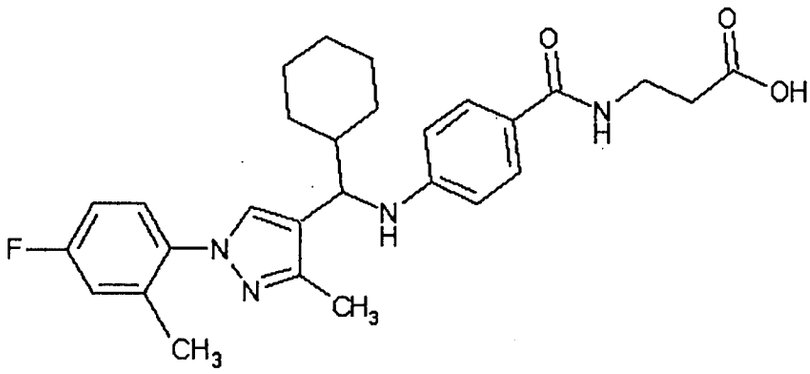
[0433]

Example 21

3-({[4-({[1-(4-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-4-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}amino)propanoic

acid

[0434]



[0435]

(1) methyl 1-(4-fluoro-2-methylphenyl)-3-methyl-1H-pyrazole-4-carboxylate

Using methyl 3-methyl-1H-pyrazole-4-carboxylate (6.25 g) synthesized in Example 1(3) and 4-fluoro-2-methylphenylboronic acid (13.9 g) and in the same manner as in Example 17(1), the title object compound (7.5 g, 68%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.26 (s, 3 H), 2.54 (s, 3 H), 3.85 (s, 3 H), 6.80 - 7.35 (m, 3 H), 7.97 (s, 1 H).

[0436]

(2) 1-(4-fluoro-2-methylphenyl)-3-methyl-1H-pyrazole-4-carbaldehyde

Methyl 1-(4-fluoro-2-methylphenyl)-3-methyl-1H-pyrazole-4-carboxylate (7.5 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (4.3 g, 83%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.24 (s, 3 H), 2.57 (s, 3 H), 6.90 - 7.39 (m, 3 H), 7.99 (s, 1 H), 10.00 (s, 1 H).

[0437]

(3) cyclohexyl[1-(4-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-4-yl]methanol

1-(4-Fluoro-2-methylphenyl)-3-methyl-1H-pyrazole-4-carbaldehyde (4.3 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound

(6.1 g, 98%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.88 - 2.00 (m, 11 H), 2.22 (s, 3 H), 2.32 (s, 3 H), 4.44 (dd, J=7.3, 3.3 Hz, 1 H), 6.91 - 7.30 (m, 3 H), 7.41 (s, 1 H).

[0438]

(4) 3-({[4-({[1-(4-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-4-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}amino)propanoic acid

Using cyclohexyl[1-(4-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-4-yl]methanol (0.50 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.55 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.52 g, 70%) was obtained as a white solid.

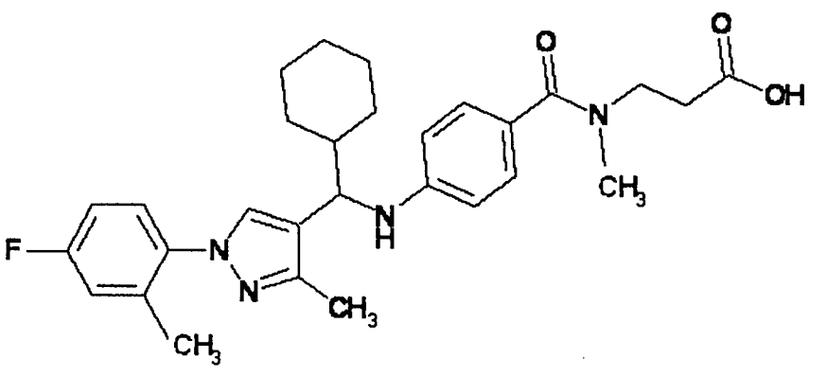
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.87 - 2.00 (m, 12 H), 2.12 (s, 3 H), 2.21 (s, 3 H), 2.34 (t, J=7.1 Hz, 2 H), 3.22 - 3.45 (m, 2 H), 4.21 (t, J=7.7 Hz, 1 H), 6.31 (d, J=8.1 Hz, 1 H), 6.59 (d, J=8.9 Hz, 2 H), 7.10 - 7.31 (m, 3 H), 7.51 (d, J=8.7 Hz, 2 H), 7.76 (s, 1 H), 8.11 (s, 1 H).

[0439]

Example 22

3-[{[4-({[1-(4-fluoro-2-methylphenyl)-3-methyl-1H-pyrazol-4-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoic acid

[0440]




[0441]

Using cyclohexyl[1-(4-fluoro-2-methylphenyl)-3-methyl-1H-

pyrazol-4-yl]methanol (0.50 g) synthesized in Example 21(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.39 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.48 g, 60%) was obtained as a white solid.

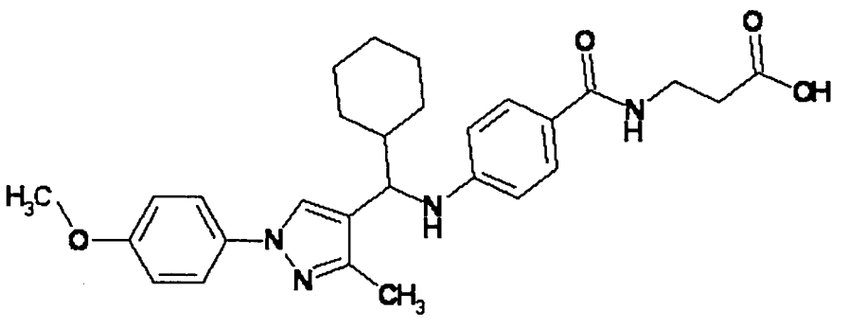
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.87 - 1.84 (m, 12 H), 2.10 (s, 3 H), 2.22 (s, 3 H), 2.48 - 2.50 (m, 2 H), 2.91 (s, 3 H), 3.52 (m, 2 H), 4.16 (d, J=9.0 Hz, 1 H), 6.59 (d, J=8.7 Hz, 2 H), 7.00 - 7.32 (m, 6 H), 7.75 (s, 1 H).

[0442]

Example 23

3-({[4-({cyclohexyl[1-(4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0443]



[0444]

(1) methyl 1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-4-carboxylate

Using methyl 3-methyl-1H-pyrazole-4-carboxylate (5.7 g) synthesized in Example 1(3) and 4-methoxyphenylboronic acid (12.4 g) and in the same manner as in Example 17(1), the title object compound (6.5 g, 65%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.55 (s, 3 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 6.97 (d, J=9.0 Hz, 2 H), 7.57 (d, J=9.0 Hz, 2 H), 8.23 (s, 1 H).

[0445]

(2) 1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-4-carbaldehyde

Methyl 1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-4-carboxylate (6.6 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound

(4.1 g, 78%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.58 (s, 3 H), 3.86 (s, 3 H), 6.99 (d, J=9.0 Hz, 2 H), 7.59 (d, J=8.9 Hz, 2 H), 8.24 (s, 1 H), 9.98 (s, 1 H).

[0446]

(3) cyclohexyl[1-(4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methanol

1-(4-Methoxyphenyl)-3-methyl-1H-pyrazole-4-carbaldehyde (4.3 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (7.1 g, 98%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.88 - 1.97 (m, 11 H), 2.33 (s, 3 H), 3.59 (br. s., 1 H), 3.83 (s, 3 H), 4.43 (dd, J=7.3, 3.0 Hz, 1 H), 6.94 (d, J=9.0 Hz, 2 H), 7.53 (d, J=9.2 Hz, 2 H), 7.70 (s, 1 H).

[0447]

(4) 3-({[4-({cyclohexyl[1-(4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

Using cyclohexyl[1-(4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methanol (0.68 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.55 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.44 g, 39%) was obtained as a white solid.

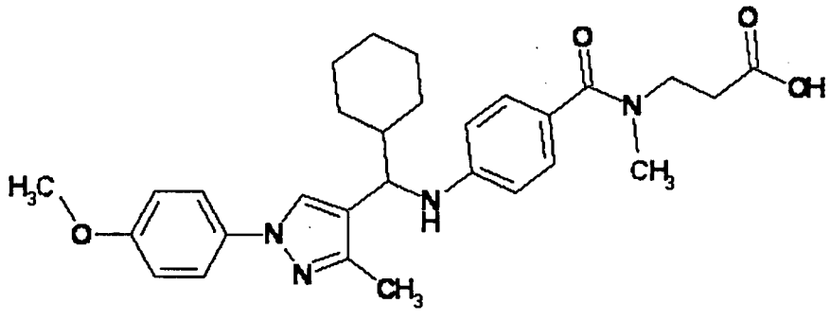
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.89 - 2.08 (m, 12 H), 2.22 (s, 3 H), 2.34 - 2.45 (m, 2 H), 3.44-3.60 (m, 2H), 3.76 (s, 3 H), 4.07 - 4.27 (m, 1 H), 6.30 (d, J=9.0 Hz, 1 H), 6.58 (d, J=8.9 Hz, 2 H), 6.99 (d, J=9.2 Hz, 2 H), 7.51 (d, J=8.9 Hz, 2 H), 7.60 (d, J=9.2 Hz, 2 H), 8.03 (br. s., 1 H), 8.14 (s, 1 H).

[0448]

Example 24

3-[{[4-({cyclohexyl[1-(4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0449]



[0450]

Using cyclohexyl[1-(4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methanol (0.68 g) synthesized in Example 23(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.42 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.28 g, 24%) was obtained as a white solid.

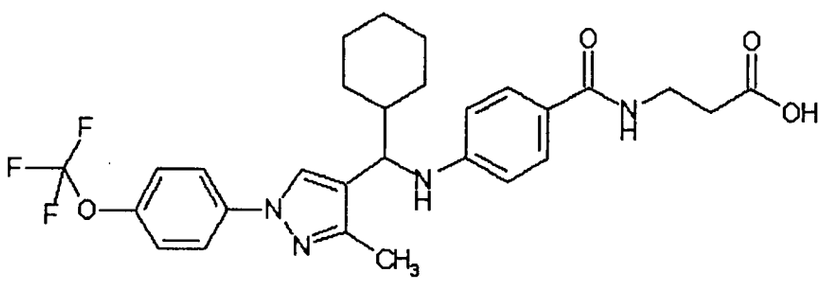
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.87 - 2.10 (m, 12 H), 2.23 (s, 3 H), 2.45-2.50 (m, 2H), 2.90 (s, 3 H), 3.44 - 3.60 (m, 2 H), 3.77 (s, 3 H), 4.13-4.15 (m, 1 H), 6.21 (d, J=7.7 Hz, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 6.99 (d, J=9.0 Hz, 2 H), 7.10 (d, J=8.7 Hz, 2 H), 7.60 (d, J=9.0 Hz, 2 H), 8.14 (s, 1 H).

[0451]

Example 25

3-[({4-[(cyclohexyl{3-methyl-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[0452]



[0453]

(1) methyl 3-methyl-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carboxylate

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Using methyl 3-methyl-1H-pyrazole-4-carboxylate (6.8 g) synthesized in Example 1(3) and 4-trifluoromethoxyphenylboronic acid (20.0 g) and in the same manner as in Example 17(1), the title object compound (3.9 g, 27%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.55 (s, 3 H), 3.86 (s, 3 H), 7.32 (d, J=9.2 Hz, 2 H), 7.71 (d, J=9.2 Hz, 2 H), 8.32 (s, 1 H).

[0454]

(2) 3-methyl-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carbaldehyde

Methyl 3-methyl-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carboxylate (3.9 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (2.3 g, 66%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.59 (s, 3 H), 7.36 (d, J=9.0 Hz, 2 H), 7.73 (d, J=9.0 Hz, 2 H), 8.32 (s, 1 H), 10.01 (s, 1 H).

[0455]

(3) cyclohexyl{3-methyl-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methanol

3-Methyl-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carbaldehyde (2.6 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (2.2 g, 72%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.89 - 1.91 (m, 11 H), 2.33 (s, 3 H), 4.44 (dd, J=7.2, 3.0 Hz, 1 H), 7.26 (d, J=9.2 Hz, 2 H), 7.66 (d, J=9.2 Hz, 2 H), 7.77 (s, 1 H).

[0456]

(4) 3-[({4-[(cyclohexyl{3-methyl-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

Using cyclohexyl{3-methyl-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methanol (0.59 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.55 g) synthesized in Example 1(2) and in the same manner as in

Example 1(7), the title object compound (0.50 g, 55%) was obtained as a white solid.

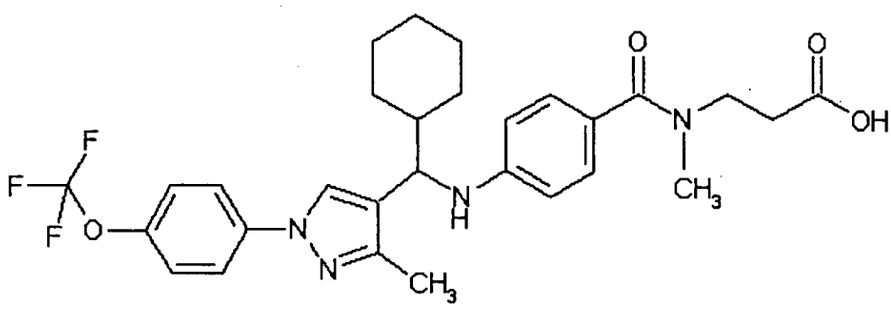
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.85 - 2.11 (m, 11 H), 2.24 (s, 3 H), 2.39 (t, J=7.2 Hz, 2 H), 3.30 - 3.43 (m, 2 H), 4.20 (t, J=7.6 Hz, 1 H), 6.34 (d, J=7.6 Hz, 1 H), 6.58 (d, J=8.3 Hz, 2 H), 7.34 - 7.61 (m, 4 H), 7.82 (d, J=9.1 Hz, 2 H), 8.02 (br. s., 1H).

[0457]

Example 26

3-[({4-[(cyclohexyl{3-methyl-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0458]



[0459]

Using cyclohexyl{3-methyl-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methanol (0.97 g) synthesized in Example 25(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.63 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (1.3 g, 63%) was obtained as a white solid.

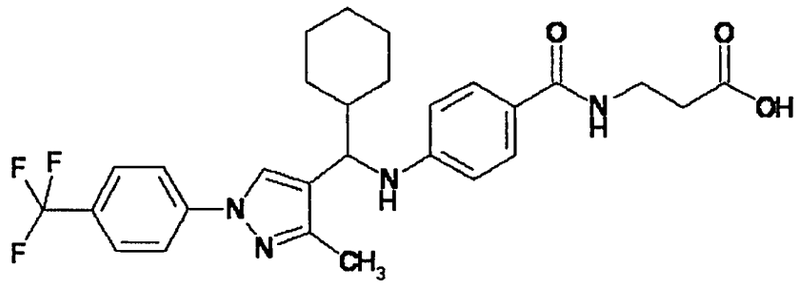
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.89 - 2.06 (m, 11 H), 2.24 (s, 3 H), 2.40 (t, J=7.0 Hz, 2 H), 3.28 - 3.45 (m, 5 H), 4.20 (t, J=7.8 Hz, 1 H), 6.34 (d, J=7.6 Hz, 1 H), 6.58 (d, J=9.1 Hz, 2 H), 7.35 - 7.57 (m, 4 H), 7.82 (d, J=9.1 Hz, 2 H), 8.01 (br s, 1 H).

[0460]

Example 27

3-[({4-[(cyclohexyl{3-methyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[0461]



[0462]

(1) methyl 3-methyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carboxylate

Using a crude product of methyl 3-methyl-1H-pyrazole-4-carboxylate (8.9 g) synthesized in Example 1(3) and 4-trifluoromethylphenylboronic acid (13.3 g) and in the same manner as in Example 17(1), the title object compound (2.0 g, 11%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.56 (s, 3 H), 3.87 (s, 3 H), 7.72 (d, J=9.2 Hz, 2 H), 7.82 (d, J=9.2 Hz, 2 H), 8.41 (s, 1 H).

[0463]

(2) 3-methyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbaldehyde

Methyl 3-methyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carboxylate (2.0 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (0.6 g, 30%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.56 (s, 3 H), 7.72 (d, J=9.0 Hz, 2 H), 7.82 (d, J=9.0 Hz, 2 H), 8.40 (s, 1 H), 9.98 (s, 1 H).

[0464]

(3) cyclohexyl{3-methyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methanol

3-Methyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbaldehyde (0.6 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (0.7 g, 93%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 1.98 (m, 11 H), 2.34 (s, 3 H), 3.53 - 3.69 (m, 1 H), 4.46 (d, J=7.0 Hz, 1 H), 7.67 (d, J=9.0 Hz, 2 H), 7.77 (d, J=9.0 Hz, 2 H), 7.85 (s, 1 H).

[0465]

(4) 3-[({4-[(cyclohexyl{3-methyl-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

Using cyclohexyl{3-methyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methanol (0.36 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.38 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (77.5 mg, 7%) was obtained as a white solid.

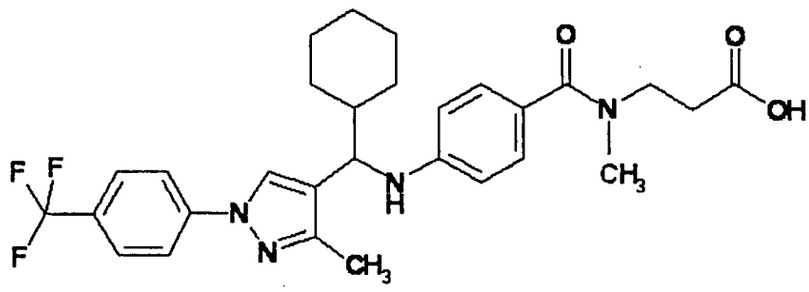
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.90 - 2.12 (m, 11 H), 2.26 (s, 3 H), 2.41 (t, J=7.2 Hz, 2 H), 3.23 - 3.44 (m, 2 H), 4.22 (t, J=7.6 Hz, 1 H), 6.36 (d, J=7.9 Hz, 1 H), 6.60 (d, J=8.9 Hz, 2 H), 7.52 - 7.80 (m, 4 H), 7.93 (d, J=6.0 Hz, 2 H), 7.97 - 8.10 (s, 1H).

[0466]

Example 28

3-[({4-[(cyclohexyl{3-methyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0467]



[0468]

Using cyclohexyl{3-methyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methanol (0.36 g) synthesized in Example 27(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate

(0.40 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.20 g, 35%) was obtained as a white solid.

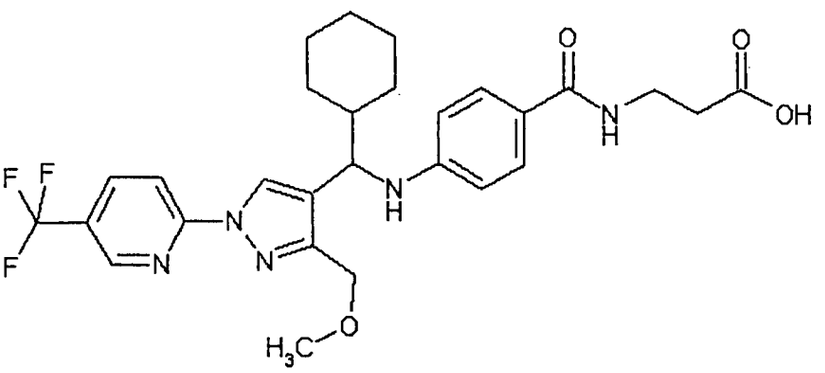
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.81 - 2.10 (m, 11 H), 2.28 (s, 3 H), 2.42 - 2.50 (m, 2 H), 2.90 (s, 3 H), 3.52 (t, J=7.3 Hz, 2 H), 4.18 (t, J=7.5 Hz, 1 H), 6.26 (d, J=7.7 Hz, 1 H), 6.59 (d, J=8.7 Hz, 2 H), 7.11 (d, J=8.7 Hz, 2 H), 7.80 (d, 2 H), 7.94 (d, J=8.5 Hz, 2 H), 8.43 (s, 1 H).

[0469]

Example 29

3-[({4-[(cyclohexyl{3-(methoxymethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[0470]



[0471]

(1) methyl 3-(methoxymethyl)-1H-pyrazole-4-carboxylate

A mixture of methyl 4-methoxyacetoacetate (25.0 g) and dimethylformamide dimethylacetal (22.9 mL) was stirred at 100°C for 2 hr, and the mixture was allowed to cool to room temperature. To the reaction mixture were added ethanol (250 mL) and hydrazine monohydrate (8.3 mL), and the mixture was heated under reflux for 12 hr. After allowing to cool, the reaction mixture was concentrated under reduced pressure, and water was added to the residue. The mixture was extracted with ethyl acetate to give a crude product (25.08 g) of methyl 3-methyl-1H-pyrazole-4-carboxylate as a pale-yellow solid. The present compound was directly used for the next reaction.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.51 (s, 3 H), 3.84 (s, 3 H),

4.85 (s, 2 H), 7.99 (s, 1 H).

[0472]

(2) methyl 3-(methoxymethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate

Using methyl 3-(methoxymethyl)-1H-pyrazole-4-carboxylate (7.4 g) synthesized above and 2-chloro-5-trifluoromethylpyridine (5.8 g) and in the same manner as in Example 1(4), the title object compound (5.2 g, 38%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.54 (s, 3 H), 3.89 (s, 3 H), 4.83 (s, 2 H), 7.90 - 8.36 (m, 2 H), 8.70 (s, 1 H), 9.06 (s, 1 H).

[0473]

(3) 3-(methoxymethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde

Methyl 3-(methoxymethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate (5.2 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (1.9 g, 40%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.53 (s, 3 H), 4.83 (s, 2 H), 8.05 - 8.25 (m, 2 H), 8.72 (s, 1 H), 9.11 (s, 1 H), 10.10 (s, 1 H).

[0474]

(4) cyclohexyl{3-(methoxymethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol

3-(Methoxymethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde (1.9 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (2.4 g, 99%) as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 2.25 (m, 11 H), 3.02 (d, J=6.0 Hz, 1 H), 3.46 (s, 3 H), 4.43 (dd, J=7.7, 6.0 Hz, 1 H), 4.52 - 4.69 (m, 2 H), 7.93 - 8.11 (m, 2 H), 8.44 (s, 1 H), 8.65 (s, 1 H).

[0475]

(5) 3-[({4-[(cyclohexyl{3-(methoxymethyl)-1-[5-

(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

Using cyclohexyl{3-(methoxymethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (1.2 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.94 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.19 g, 10%) was obtained as a white solid.

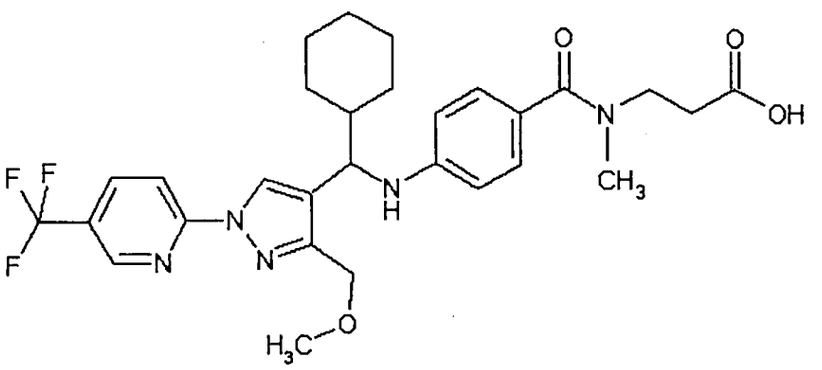
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 1.90 - 2.10 (m, 11 H), 2.40 (t, J=7.2 Hz, 2 H), 3.24 - 3.45 (m, 5 H), 4.28 - 4.71 (m, 3 H), 6.37 (d, J=8.9 Hz, 1 H), 6.64 (d, J=8.9 Hz, 2 H), 7.51 (d, J=8.9 Hz, 2 H), 8.00 (d, J=8.9 Hz, 2 H), 8.33 (dd, J=9.0, 2.3 Hz, 1 H).

[0476]

Example 30

3-[({4-[(cyclohexyl{3-(methoxymethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0477]




[0478]

Using cyclohexyl{3-(methoxymethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (1.2 g) synthesized in Example 29(4) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (1.0 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.17 g, 8%) was obtained as a white solid.

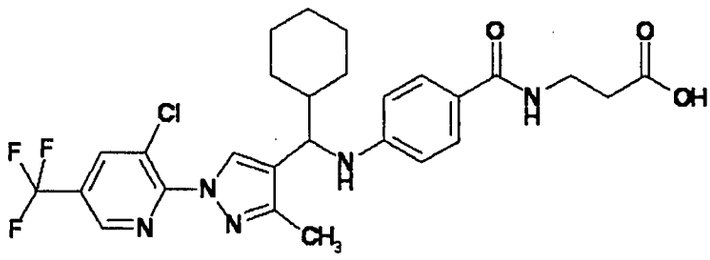
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.89 - 2.09 (m, 11 H), 2.40 - 2.52 (m, 2 H), 2.89 (s, 3 H), 3.33 (s, 3 H), 3.51 (t, J=7.3 Hz, 2 H), 4.28 - 4.74 (m, 3 H), 6.27 (d, J=8.7 Hz, 1 H), 6.64 (d, J=8.7 Hz, 2 H), 7.09 (d, J=8.7 Hz, 2 H), 8.01 (d, J=8.9 Hz, 1 H), 8.33 (dd, J=9.0, 2.3 Hz, 1 H), 8.58 (s, 1 H), 8.83 (s, 1 H).

[0479]

Example 31

3-{[(4-{[{1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-3-methyl-1H-pyrazol-4-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0480]



[0481]

(1) methyl 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-3-methyl-1H-pyrazole-4-carboxylate

Using methyl 3-methyl-1H-pyrazole-4-carboxylate (3.8 g) synthesized in Example 1(3) and 2,3-dichloro-5-trifluoromethylpyridine (5.8 g) and in the same manner as in Example 1(4), the title object compound (7.0 g, 78%) was obtained as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.60 (s, 3 H), 3.88 (s, 3 H), 8.16 (d, J=1.5 Hz, 1 H), 8.67 - 8.72 (m, 2 H).

[0482]

(2)1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-3-methyl-1H-pyrazole-4-carbaldehyde

To a solution (150 mL) of methyl 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-3-methyl-1H-pyrazole-4-carboxylate (7.0 g) synthesized above in tetrahydrofuran was

added dropwise diisobutylaluminum hydride (1.5M toluene solution, 58.4 mL) at 0°C. After stirring for 30 min, the reaction mixture was poured into 2N hydrochloric acid of 0°C, and the mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate, and the solvent was evaporated. The residue was treated in the same manner as in Example 1(5) to give the title object compound (1.7 g, 27%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.63 (s, 3 H), 8.19 (s, 1 H), 8.70 - 8.73 (m, 2 H), 10.07 (s, 1 H).

[0483]

(3){1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-3-methyl-1H-pyrazol-4-yl}(cyclohexyl)methanol

1-[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]-3-methyl-1H-pyrazole-4-carbaldehyde (1.7 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (1.5 g, 66%) as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 2.02 (m, 11 H), 2.39 (s, 3 H), 4.47 (d, J=7.2 Hz, 1 H), 8.05 - 8.14 (m, 1 H), 8.18 (s, 1 H), 8.66 (s, 2 H).

[0484]

(4)3-{[(4-{[{1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-3-methyl-1H-pyrazol-4-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

Using {1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-3-methyl-1H-pyrazol-4-yl}(cyclohexyl)methanol (0.74 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.57 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.11 g, 10%) was obtained as an amorphous pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 - 1.98 (m, 11 H), 2.37 (s, 3 H), 2.50 - 2.72 (m, 2 H), 3.44 - 3.75 (m, 2 H), 4.24 (d, J=6.2 Hz, 1 H), 6.51 (d, J=8.1 Hz, 2 H), 6.66 (br. s., 1 H), 6.89

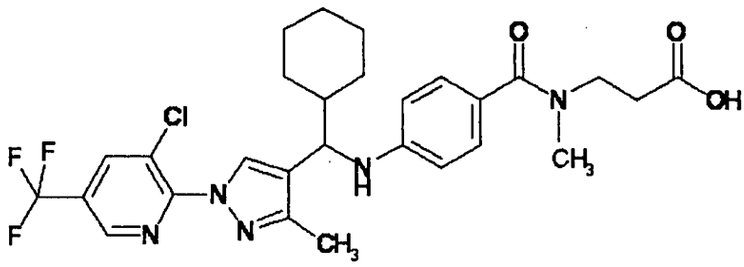
(br. s., 1 H), 7.52 (d, J=8.1 Hz, 2 H), 7.98 - 8.20 (m, 2 H), 8.60 (s, 1 H).

[0485]

Example 32

3-{[(4-{[{1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-3-methyl-1H-pyrazol-4-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[0486]



[0487]

Using {1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-3-methyl-1H-pyrazol-4-yl}(cyclohexyl)methanol (0.74 g) synthesized in Example 31(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.60 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (54.4 mg, 5%) was obtained as an amorphous pale-yellow solid.

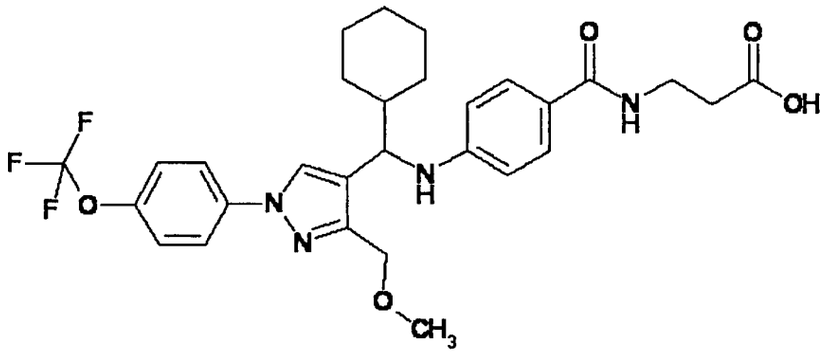
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.98 (m, 11 H), 2.36 (s, 3 H), 2.58 - 2.74 (m, 2 H), 3.04 (s, 3 H), 3.59 - 3.82 (m, 2 H), 4.23 (d, J=6.0 Hz, 1 H), 6.55 (d, J=8.5 Hz, 2 H), 7.01 (br. s., 1 H), 7.21 (d, J=8.5 Hz, 2 H), 8.08 (s, 1 H), 8.13 (s, 1 H), 8.63 (s, 1 H).

[0488]

Example 33

3-[({4-[(cyclohexyl{3-(methoxymethyl)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[0489]



[0490]

(1) methyl 3-(methoxymethyl)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carboxylate

Using methyl 4-methoxyacetoacetate (3.2 g), dimethylformamide dimethylacetal (2.9 mL) and 4-trifluoromethoxyphenylhydrazine hydrochloride (5.0 g) and in the same manner as in Example 15(1), the title object compound (3.4 g, 47%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.46 (s, 3 H), 3.89 (s, 3 H), 4.70 (s, 2 H), 7.37 (d, J=9.0 Hz, 2H), 7.73 (d, J=9.0 Hz, 2H), 8.08 (s, 1 H).

[0491]

(2) 3-(methoxymethyl)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carbaldehyde

Methyl 3-(methoxymethyl)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carboxylate (3.4 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (2.9 g, 93%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.41 (s, 3 H), 4.70 (s, 2 H), 7.37 - 8.08 (m, 5 H), 10.00 (s, 1 H).

[0492]

(3)cyclohexyl{3-(methoxymethyl)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methanol

3-(Methoxymethyl)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carbaldehyde (2.9 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (2.8 g, 77%) as a pale-yellow solid.

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$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.73 - 2.28 (m, 11 H), 3.41 (s, 3 H), 4.30 - 4.53 (m, 3 H), 7.33 (d, J=8.5 Hz, 2 H), 7.55 - 7.75 (m, 3 H).

[0493]

(4) 3-[({4-[(cyclohexyl{3-(methoxymethyl)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

Using cyclohexyl{3-(methoxymethyl)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methanol (0.75 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.55 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.43 g, 39%) was obtained as a colorless solid.

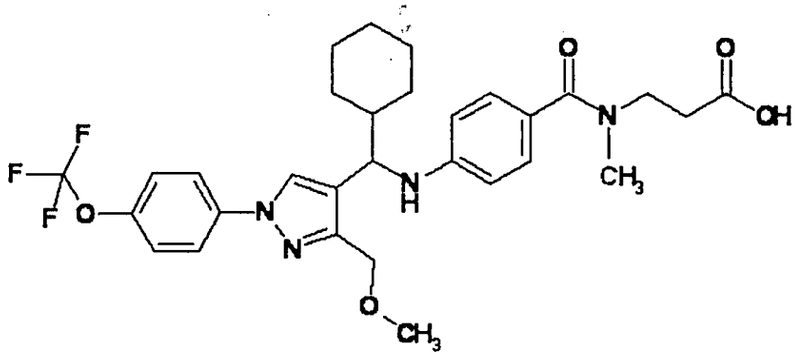
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.90 - 2.08 (m, 11 H), 2.43 (t, J=7.1 Hz, 2 H), 3.25 - 3.49 (m, 5 H), 4.29 - 4.31 (m, 1 H), 4.39 - 4.59 (m, 2 H), 6.43 (d, J=8.5 Hz, 1 H), 6.63 (d, J=8.9 Hz, 2 H), 7.45 - 7.58 (m, 4 H), 7.63 - 7.77 (m, 3 H), 7.94 - 8.09 (m, 1 H).

[0494]

Example 34

3-[({4-[(cyclohexyl{3-(methoxymethyl)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0495]




[0496]

Using cyclohexyl{3-(methoxymethyl)-1-[4-

(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methanol (0.75 g) synthesized in Example 33(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.59 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.42 g, 39%) was obtained as a colorless solid.

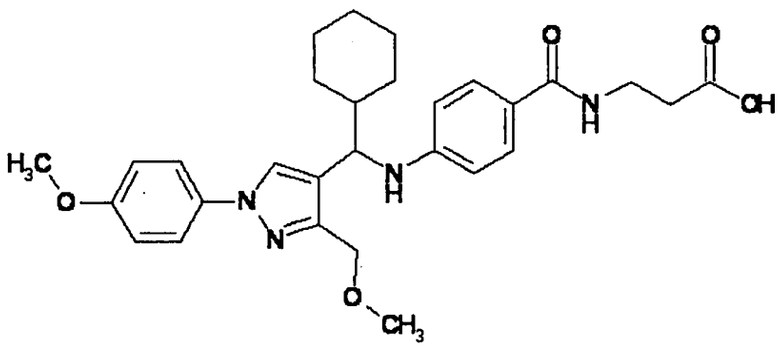
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.87 - 2.12 (m, 11 H), 2.40 - 2.50 (m, 2 H), 2.90 (s, 3 H), 3.31 (s, 3 H), 3.52 (t, J=7.2 Hz, 2 H), 4.21 - 4.36 (m, 1 H), 4.36 - 4.59 (m, 2 H), 6.32 (d, J=8.7 Hz, 1 H), 6.62 (d, J=8.7 Hz, 2 H), 7.09 (d, J=8.5 Hz, 2 H), 7.51 (d, J=8.5 Hz, 2 H), 7.64 - 7.79 (m, 3 H).

[0497]

Example 35

3-({[4-({cyclohexyl[3-(methoxymethyl)-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0498]



[0499]

(1) methyl 3-(methoxymethyl)-1-(4-methoxyphenyl)-1H-pyrazole-4-carboxylate

Using methyl 4-methoxyacetoacetate (5.8 g), dimethylformamide dimethylacetal (5.4 mL) and 4-methoxyphenylhydrazine hydrochloride (7.0 g) and in the same manner as in Example 15(1), the title object compound (5.5 g, 50%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.42 (s, 3 H), 3.87 (s, 3 H), 3.88 (s, 3 H), 4.64 (s, 2 H), 7.00 (d, J=9.0 Hz, 2H), 7.53 (d, J=9.0 Hz, 2H), 8.05 (s, 1 H).

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[0500]

(2) 3-(methoxymethyl)-1-(4-methoxyphenyl)-1H-pyrazole-4-carbaldehyde

Methyl 3-(methoxymethyl)-1-(4-methoxyphenyl)-1H-pyrazole-4-carboxylate (2.8 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (2.0 g, 83%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.42 (s, 3 H), 3.87 (s, 3 H), 4.64 (s, 2 H), 7.00 - 8.05 (m, 5 H), 10.00 (s, 1 H).

[0501]

(3) cyclohexyl[3-(methoxymethyl)-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methanol

3-(Methoxymethyl)-1-(4-methoxyphenyl)-1H-pyrazole-4-carbaldehyde (2.0 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (2.1 g, 77%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.73 - 2.28 (m, 11 H), 3.36 (s, 3 H), 3.86 (s, 3 H), 4.30 - 4.53 (m, 3 H), 6.97 (d, J=8.9 Hz, 2 H), 7.44 (d, J=8.9 Hz, 2 H), 7.59 (s, 1H).

[0502]

(4) 3-({[4-({cyclohexyl[3-(methoxymethyl)-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

Using cyclohexyl[3-(methoxymethyl)-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methanol (0.75 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.54 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.39 g, 33%) was obtained as a white solid.

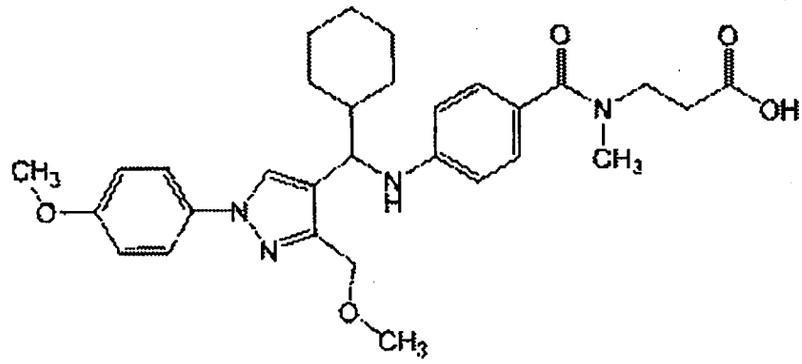
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.89 - 2.11 (m, 11 H), 2.44 (t, J=7.2 Hz, 2 H), 3.32 - 3.46 (m, 2 H), 3.80 (s, 3 H), 4.22 - 4.56 (m, 3 H), 6.40 (d, J=8.7 Hz, 1 H), 6.62 (d, J=8.9 Hz, 2 H), 7.04 (d, J=9.0 Hz, 2 H), 7.36 - 7.55 (m, 4 H), 7.57 (s, 1 H), 8.01 (s, 1 H).

[0503]

Example 36

3-[{[4-({cyclohexyl[3-(methoxymethyl)-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0504]



[0505]

Using cyclohexyl[3-(methoxymethyl)-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methanol (0.75 g) synthesized in Example 35(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.57 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.44 g, 36%) was obtained as a white solid.

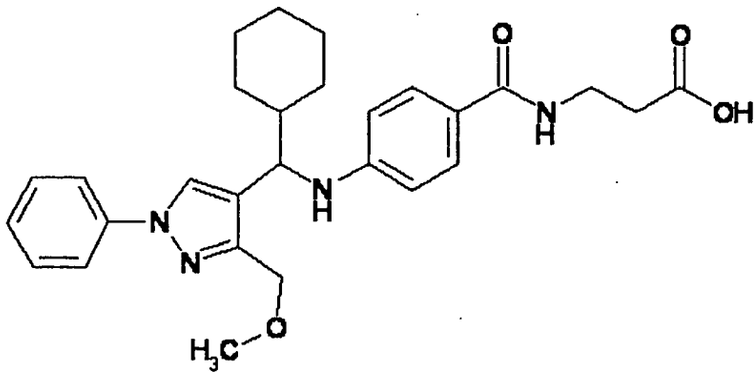
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.90 - 2.12 (m, 11 H), 2.42 - 2.50 (m, 2 H), 2.91 (s, 3 H), 3.26 (s, 3 H), 3.52 (t, J=7.4 Hz, 2 H), 3.80 (s, 3 H), 4.14 - 4.54 (m, 3 H), 6.29 (d, J=8.5 Hz, 1 H), 6.62 (d, J=8.7 Hz, 2 H), 6.97 - 7.19 (m, 4 H), 7.44 (d, J=8.9 Hz, 2 H), 7.58 (s, 1 H).

[0506]

Example 37

3-({[4-({cyclohexyl[3-(methoxymethyl)-1-phenyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0507]



[0508]

(1) methyl 3-(methoxymethyl)-1-phenyl-1H-pyrazole-4-carboxylate

Using methyl 4-methoxyacetoacetate (7.9 g), dimethylformamide dimethylacetal (7.2 mL) and phenylhydrazine hydrochloride (5.8 g) and in the same manner as in Example 15(1), the title object compound (7.3 g, 55%) was obtained as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.44 (s, 3 H), 3.89 (s, 3 H), 4.68 (s, 2 H), 7.30 - 7.70 (m, 5 H), 8.08 (s, 1 H).

[0509]

(2) 3-(methoxymethyl)-1-phenyl-1H-pyrazole-4-carbaldehyde

Methyl 3-(methoxymethyl)-1-phenyl-1H-pyrazole-4-carboxylate (3.5 g) synthesized above was treated in the same manner as in Example 1(5) to give the title object compound (2.5 g, 82%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.45 (s, 3 H), 4.67 (s, 2 H), 7.40 - 8.20 (m 6 H), 10.08 (s, 1 H).

[0510]

(3) cyclohexyl[3-(methoxymethyl)-1-phenyl-1H-pyrazol-4-yl]methanol

3-(Methoxymethyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (2.5 g) synthesized above was treated in the same manner as in Example 1(6) to give the title object compound (3.1 g, 75%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.73 - 2.40 (m, 11 H), 3.38 (s, 3

H), 4.40 (s, 2 H), 4.42 - 4.55 (m, 1 H), 7.27 - 7.70 (m, 6H).

[0511]

(4) 3-({[4-({cyclohexyl[3-(methoxymethyl)-1-phenyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

Using cyclohexyl[3-(methoxymethyl)-1-phenyl-1H-pyrazol-4-yl]methanol (0.50 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.39 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.37 g, 46%) was obtained as a white solid.

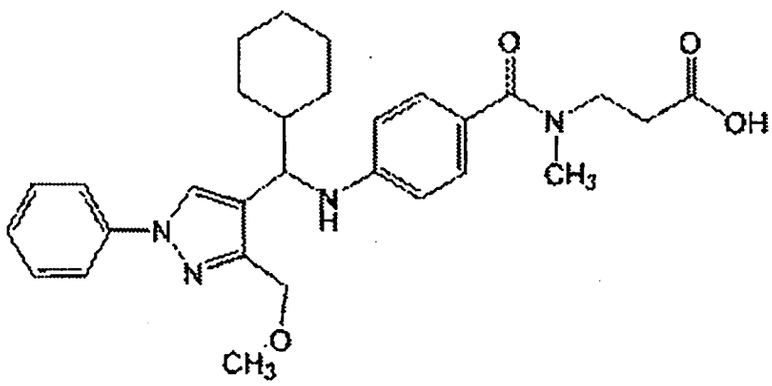
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 - 2.17 (m, 11 H), 2.58 - 2.78 (m, 2 H), 3.34 (s, 3 H), 3.58 - 3.76 (m, 2 H), 4.21 - 4.51 (m, 3 H), 6.51 - 6.71 (m, 3 H), 7.36 - 7.74 (m, 8 H).

[0512]

Example 38

3-[{[4-({cyclohexyl[3-(methoxymethyl)-1-phenyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0513]



[0514]

Using cyclohexyl[3-(methoxymethyl)-1-phenyl-1H-pyrazol-4-yl]methanol (0.50 g) synthesized in Example 37(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.42 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.33 g, 39%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 - 2.11 (m, 11 H), 2.61 -

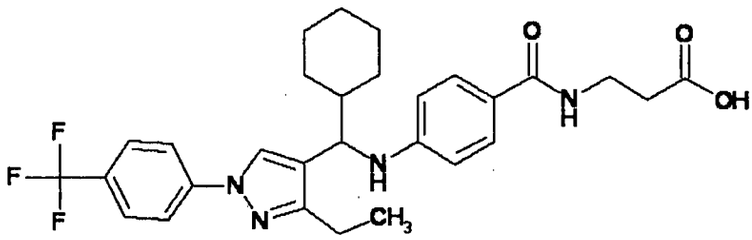
2.79 (m, 2 H), 3.07 (s, 3 H), 3.34 (s, 3 H), 3.72 (t, J=6.5 Hz, 2 H), 4.25 - 4.46 (m, 3 H), 6.57 (d, J=8.5 Hz, 2 H), 7.35 - 7.61 (m, 8 H).

[0515]

Example 39

3-[({4-[(cyclohexyl{3-ethyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[0516]



[0517]

(1) methyl 3-ethyl-1H-pyrazole-4-carboxylate

Using methyl 3-oxopentanoate (6.5 g) and in the same manner as in Example 1(3), the title object compound (7.0 g, 91%) was obtained as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.32 (t, J=7.6 Hz, 3 H), 3.02 (q, J=7.6 Hz, 2 H), 3.84 (s, 3 H), 7.96 (s, 1 H), 11.28 (br. s., 1 H).

[0518]

(2) methyl 3-ethyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carboxylate

Using methyl 3-ethyl-1H-pyrazole-4-carboxylate (4.6 g) synthesized above and in the same manner as in Example 17(1), the title object compound (6.0 g, 67%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.33 (t, J=7.4 Hz, 3 H), 2.99 (q, J=7.5 Hz, 2 H), 3.87 (s, 3 H), 7.71-7.74 (m, 2 H), 7.82-7.85 (m, 2 H), 8.41 (s, 1 H).

[0519]

(3) 3-ethyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbaldehyde

Using methyl 3-ethyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carboxylate (6.0 g) synthesized above and in the same manner as in Example 1(5), the title object compound (4.2 g, 78%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.37 (t, J=7.4 Hz, 3 H), 3.00 (q, J=7.4 Hz, 2 H), 7.74-7.77 (m, 2H), 7.84-7.87 (m, 2 H), 8.42 (s, 1 H), 10.03 (s, 1 H).

[0520]

(4) cyclohexyl{3-ethyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methanol

Using 3-ethyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbaldehyde (1.6 g) synthesized above and in the same manner as in Example 1(6), the title object compound (1.9 g, 91%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86-1.43 (m, 8 H), 1.52-1.90 (m, 5 H), 2.05 (br.s, 1 H), 2.72 (q, J=7.5 Hz, 2 H), 4.46 (dd, J=7.2, 3.0 Hz, 1 H), 7.60-7.71 (m, 2 H), 7.71-7.82 (m, 2 H), 7.86 (s, 1 H).

[0521]

(5) 3-({4-[(cyclohexyl{3-ethyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methyl)amino]benzoyl}amino)propanoic acid

Using cyclohexyl{3-ethyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methanol (0.90 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.75 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (82 mg, 6%) was obtained as a white solid.

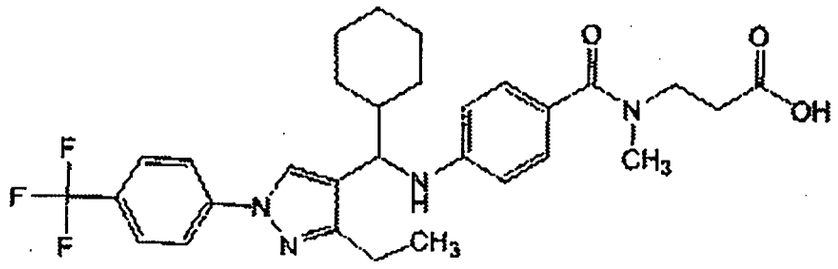
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.09-1.32 (m, 8 H), 1.45-1.83 (m, 5 H), 1.93-2.11 (m, 1 H), 2.37 (t, J=7.0 Hz, 2 H), 2.68 (qd, J=7.5, 4.0 Hz, 2 H), 3.35 (q, J=5.7 Hz, 2 H), 4.23 (t, J=7.8 Hz, 1 H), 6.33 (d, J=7.9 Hz, 1 H), 6.60 (d, J=8.7 Hz, 2 H), 7.52 (d, J=8.9 Hz, 2 H), 7.81 (d, J=8.7 Hz, 2 H), 7.87-7.98 (m, 2 H), 7.98-8.12 (m, 1 H), 8.43 (s, 1 H).

[0522]

Example 40

3-[({4-[(cyclohexyl{3-ethyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0523]



[0524]

Using cyclohexyl{3-ethyl-1-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}methanol (0.90 g) synthesized in Example 39(4) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.75 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (85 mg, 6%) was obtained as a white solid.

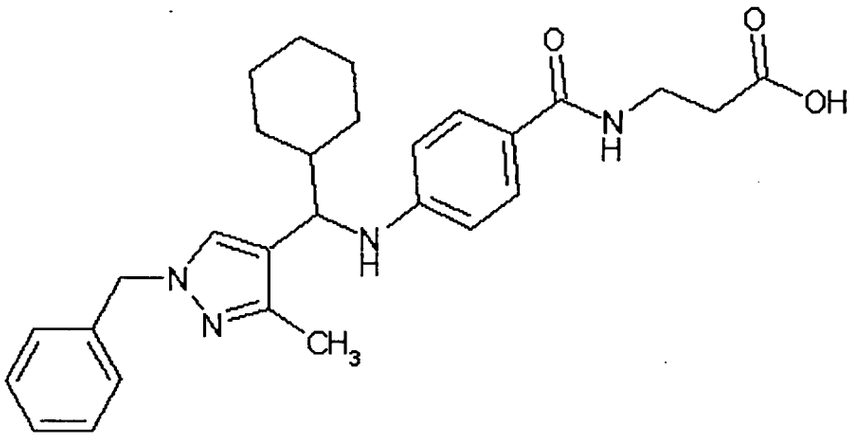
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.88-1.24 (m, 8 H), 1.46-1.80 (m, 5 H), 1.92-2.09 (m, 1 H), 2.46 (t, J=7.5 Hz, 2 H), 2.68 (qd, J=7.5, 3.3 Hz, 2 H), 2.98 (s, 3 H), 3.50 (t, J=7.2 Hz, 2 H), 4.20 (t, J=7.4 Hz, 1 H), 6.22 (d, J=7.7 Hz, 1 H), 6.60 (d, J=8.5 Hz, 2 H), 7.10 (d, J=8.7 Hz, 2 H), 7.81 (d, J=8.7 Hz, 2 H), 7.86-8.05 (m, 2 H), 8.43 (s, 1 H).

[0525]

Example 41

3-{[(4-{[(1-benzyl-3-methyl-1H-pyrazol-4-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0526]



[0527]

(1) methyl 1-benzyl-3-methyl-1H-pyrazole-4-carboxylate

Methyl 3-methyl-1H-pyrazole-4-carboxylate (5.1 g) synthesized in Example 1(3) was dissolved in dimethylformamide (50 mL), potassium carbonate (5.3 g) and benzylbromide (4.6 mL) were added to at room temperature, and the mixture was stirred overnight. The reaction mixture was poured into water, and the mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (5.9 g, 71%) as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.48 (s, 3 H), 3.78 (s, 3 H), 5.22 (s, 2 H), 6.96 - 7.45 (m, 5 H), 7.77 (s, 1 H).

[0528]

(2) 1-benzyl-3-methyl-1H-pyrazole-4-carbaldehyde

Using methyl 1-benzyl-3-methyl-1H-pyrazole-4-carboxylate (5.9 g) synthesized above and in the same manner as in Example 1(5), the title object compound (5.0 g, 96%) was obtained as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.50 (s, 3 H), 5.25 (s, 2 H), 6.96 - 7.45 (m, 5 H), 7.76 (s, 1 H), 9.85 (s, 1H).

(3) (1-benzyl-3-methyl-1H-pyrazol-4-yl)(cyclohexyl)methanol

Using 1-benzyl-3-methyl-1H-pyrazole-4-carbaldehyde (5.0 g) synthesized above and in the same manner as in Example 1(6),

the title object compound (3.3 g, 47%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.75 - 1.97 (m, 11 H), 2.25 (s, 3 H), 4.34 (d, J=7.4, 3.3 Hz, 1 H), 5.20 (s, 2H), 7.00 - 7.50 (m, 6 H).

[0529]

(4) 3-{[(4-{[(1-benzyl-3-methyl-1H-pyrazol-4-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

Using (1-benzyl-3-methyl-1H-pyrazol-4-yl)(cyclohexyl)methanol (1.0 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.62 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (28.6 mg, 4%) was obtained as a white solid.

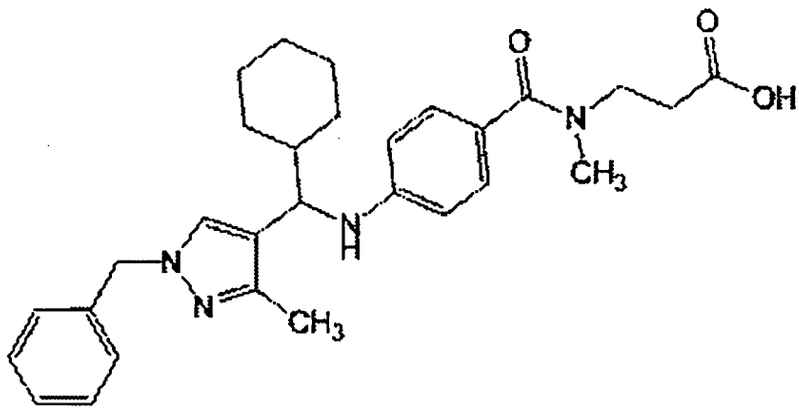
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.77 - 2.01 (m, 11 H), 2.12 (s, 3 H), 2.38 - 2.46 (m, 2 H), 3.35 - 3.44 (m, 2 H), 3.99 - 4.21 (m, 1 H), 5.11 - 5.19 (m, 2 H), 6.25 (d, J=9.0 Hz, 1 H), 6.52 (d, J=8.7 Hz, 2 H), 7.04 (dd, J=7.5, 1.9 Hz, 2 H), 7.25 - 7.60 (m, 6 H), 7.99 (s, 1 H).

[0530]

Example 42

3-{[(4-{[(1-benzyl-3-methyl-1H-pyrazol-4-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[0531]



[0532]

Using (1-benzyl-3-methyl-1H-pyrazol-4-yl)(cyclohexyl)methanol (0.65 g) synthesized in Example 41(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.65 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (18.2 mg, 2%) was obtained as a white solid.

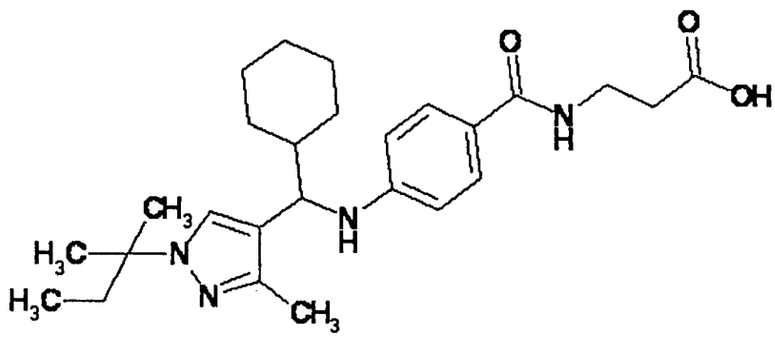
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 1.14 - 2.00 (br. s., 11 H), 2.13 (s, 3 H), 2.38 - 2.46 (m, 2 H), 2.90 (s, 3 H), 3.42 - 3.60 (m, 2 H), 4.00 - 4.17 (m, 1 H), 5.16 (s, 2 H), 6.17 (d, J=6.0 Hz, 1 H), 6.52 (d, J=8.5 Hz, 2 H), 6.95 - 7.36 (m, 7 H), 7.52 (s, 1 H).

[0533]

Example 43

3-({[4-({cyclohexyl[1-(1,1-dimethylpropyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0534]



[0535]

(1) methyl 1-(1,1-dimethylpropyl)-3-methyl-1H-pyrazole-4-carboxylate

Methyl 3-methyl-1H-pyrazole-4-carboxylate (10.8 g) synthesized in Example 1(3) was dissolved in acetonitrile (100 mL), 2-methyl-2-butene (16.3 mL) and p-toluenesulfonic acid monohydrate (4.4 g) were added, and the mixture was stirred in a sealed tube at 120°C for 4 hr. The reaction mixture was poured into aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was

concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (4.6 g, 29%) as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.68 (t, J=7.5 Hz, 3 H), 1.53 (s, 6 H), 1.88 (q, J=7.5 Hz, 2 H), 2.46 (s, 3 H), 3.80 (s, 3 H), 7.90 (s, 1 H).

[0536]

(2) 1-(1,1-dimethylpropyl)-3-methyl-1H-pyrazole-4-carbaldehyde

Using methyl 1-(1,1-dimethylpropyl)-3-methyl-1H-pyrazole-4-carboxylate (4.6 g) synthesized above and in the same manner as in Example 1(5), the title object compound (3.0 g, 73%) was obtained as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.68 (t, J=7.5 Hz, 3 H), 1.53 (s, 6 H), 1.88 (q, J=7.5 Hz, 2 H), 2.46 (s, 3 H), 7.90 (s, 1 H), 9.85 (s, 1H).

[0537]

(3) cyclohexyl[1-(1,1-dimethylpropyl)-3-methyl-1H-pyrazol-4-yl]methanol

Using 1-(1,1-dimethylpropyl)-3-methyl-1H-pyrazole-4-carbaldehyde (3.0 g) synthesized above and in the same manner as in Example 1(6), the title object compound (1.4 g, 32%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.67 (t, J=7.4 Hz, 3 H), 0.88 - 2.00 (m, 13 H), 1.52 (s, 6 H), 2.24 (s, 3 H), 3.61 (br. s., 1 H), 4.34 (dd, J=7.6, 2.0 Hz, 1 H), 7.34 (s, 1 H).

[0538]

(4) 3-({[4-({cyclohexyl[1-(1,1-dimethylpropyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

Using cyclohexyl[1-(1,1-dimethylpropyl)-3-methyl-1H-pyrazol-4-yl]methanol (1.0 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.67 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.41 g, 46%) was obtained as a white solid.

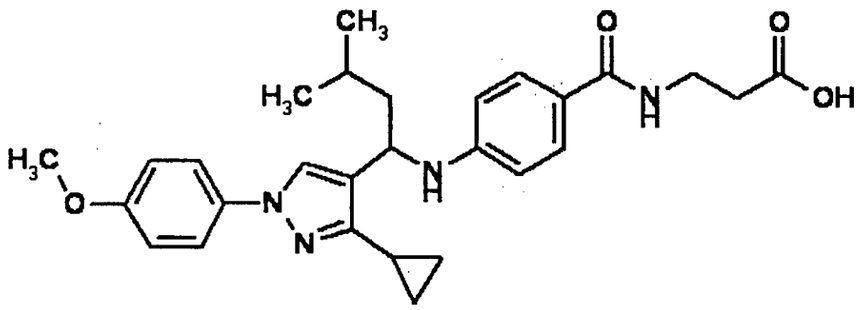
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.56 (t, J=7.6 Hz, 3 H), 0.88 - 1.35 (m, 5 H), 1.48 (s, 6 H), 1.55 - 1.98 (m, 8 H), 2.26 (s, 3 H), 2.67 (t, J=5.9 Hz, 2 H), 3.68 (q, J=5.8 Hz, 2 H), 4.12 (d, J=6.1 Hz, 1 H), 6.46 (d, J=8.7 Hz, 2 H), 6.66 (t, J=6.2 Hz, 1 H), 7.19 (s, 1 H), 7.53 (d, J=9.1 Hz, 2 H).

[0539]

Example 44

3-({[4-({1-[3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]-3-methylbutyl}amino)phenyl]carbonyl}amino)propanoic acid

[0540]



[0541]

(1) methyl 3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazole-4-carboxylate

Using methyl 3-cyclopropyl-3-oxopropanoate (3.7 g), dimethylformamide dimethylacetal (3.6 mL) and p-methoxyphenylhydrazine monohydrate (4.7 g) and in the same manner as in Example 15(1), the title object compound (5.9 g, 84%) was obtained as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.60 - 1.01 (m, 4 H), 1.86 - 2.01 (m, 1 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 6.98 (d, J=8.9 Hz, 2 H), 7.41 (d, J=9.0 Hz, 2 H), 7.98 (s, 1 H).

[0542]

(2) 3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazole-4-carbaldehyde

Using methyl 3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazole-4-carboxylate (5.9 g) synthesized above and in the same manner as in Example 1(5), the title object compound (3.6 g, 68%) was obtained as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.73 - 1.10 (m, 4 H), 1.87 - 2.07 (m, 1 H), 3.88 (s, 3 H), 7.01 (d, J=8.9 Hz, 2 H), 7.44 (d, J=8.9 Hz, 2 H), 8.03 (s, 1 H), 10.03 (s, 1 H).

[0543]

(3) 1-[3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]-3-methylbutan-1-ol

3-Cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazole-4-carbaldehyde (1.8 g) synthesized above was dissolved in tetrahydrofuran (10 mL), isobutylmagnesium bromide (1M tetrahydrofuran solution, 12 mL) was added dropwise at 0°C. In the same manner as in Example 1(6), the title object compound (1.8 g, 82%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.36 - 0.91 (m, 5 H), 0.99 (d, J=6.4 Hz, 6 H), 1.48 - 1.97 (m, 3 H), 3.86 (s, 3 H), 4.89 - 5.05 (m, 1 H), 6.96 (d, J=9.0 Hz, 2 H), 7.42 (d, J=9.0 Hz, 2 H), 7.60 (s, 1 H).

[0544]

(4) 3-({[4-({1-[3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]-3-methylbutyl}amino)phenyl]carbonyl}amino)propanoic acid

Using 1-[3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]-3-methylbutan-1-ol (0.5 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.31 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (23 mg, 3%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.42 - 0.84 (m, 4 H), 0.99 (dd, J=13.8, 5.7 Hz, 6 H), 1.60 -1.80 (m, 4 H), 2.60 - 2.65 (m., 2 H), 3.64 - 3.66 (m., 2 H), 3.84 (s, 3 H), 4.69 (s, 1 H), 6.55 (d, J=8.5 Hz, 2 H), 6.70 (br. s., 1 H), 6.94 (d, J=8.8 Hz, 2 H), 7.39 (d, J=8.8 Hz, 2 H), 7.50 (s, 1 H), 7.58 (d, J=8.5 Hz, 2 H).

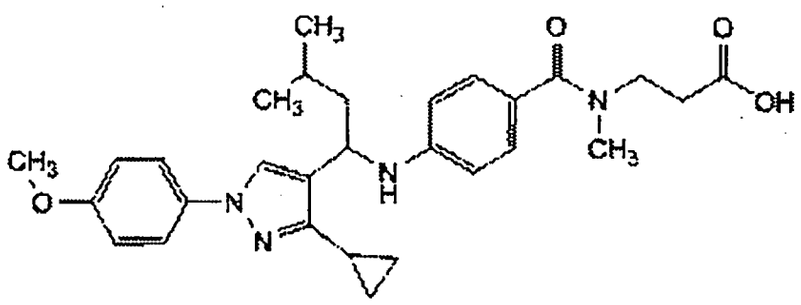
[0545]

Example 45

3-[{[4-({1-[3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]-3-

methylbutyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0546]



[0547]

Using 1-[3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]-3-methylbutan-1-ol (0.5 g) synthesized in Example 44(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.33 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (80 mg, 9%) was obtained as a white solid.

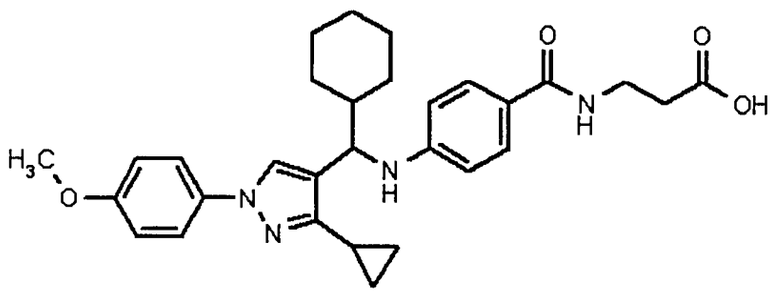
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.34 - 0.90 (m, 4 H), 0.99 (dd, J=14.0, 4.8 Hz, 6 H), 1.70 - 2.00 (m, 4 H), 2.71 (br. s., 2 H), 3.10 (s, 3 H), 3.74 (s, 2 H), 3.85 (s, 3 H), 4.68 (br. s., 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.95 (dd, J=8.7, 1.3 Hz, 2 H), 7.31 - 7.40 (m, 4 H), 7.50 (s, 1 H).

[0548]

Example 46

3-({[4-({cyclohexyl[3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0549]



[0550]

(1) cyclohexyl[3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazol-4-

yl]methanol

Using 3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazole-4-carbaldehyde (1.8 g) synthesized in Example 44(2) and in the same manner as in Example 1(6), the title object compound (2.1 mg, 85%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.29 - 2.27 (m, 16 H), 3.86 (s, 3 H), 4.57 (dd, J=8.1, 4.0 Hz, 1 H), 6.96 (d, J=9.0 Hz, 2 H), 7.42 (d, J=8.9 Hz, 2 H), 7.59 (s, 1 H).

[0551]

(2) 3-({[4-({cyclohexyl[3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

Using cyclohexyl[3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methanol (0.5 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.36 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (43 mg, 5%) was obtained as a white solid.

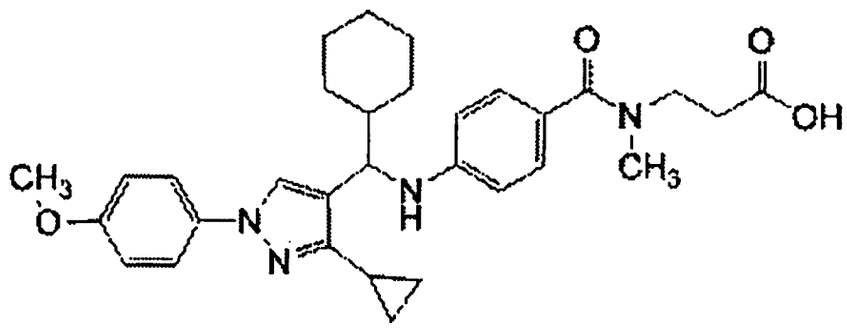
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.30 - 2.20 (m., 16 H), 2.65 (br. s., 2 H), 3.66 (br. s., 2 H), 3.85 (s, 3 H), 4.45 (d, J=7.2 Hz, 1 H), 6.55 (d, J=8.9 Hz, 2 H), 6.60 - 6.69 (m, 1 H), 6.94 (d, J=9.0 Hz, 2 H), 7.38 (d, J=9.0 Hz, 2 H), 7.47 (s, 1 H), 7.56 (d, J=8.9 Hz, 2 H).

[0552]

Example 47

3-[{[4-({cyclohexyl[3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0553]



[0554]

Using cyclohexyl[3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methanol (0.5 g) synthesized in Example 46(1) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.38 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.11 g, 14%) was obtained as a white solid.

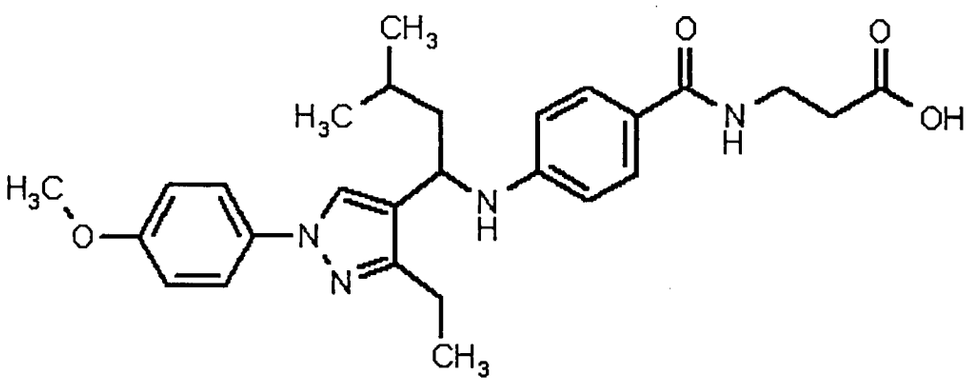
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.31 - 2.00 (m, 16 H), 2.70 - 2.74 (m, 2 H), 3.10 (s, 3 H), 3.74 (t, J=6.5 Hz, 2 H), 3.85 (s, 3 H), 4.45 (d, J=6.8 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.95 (d, J=9.0 Hz, 2 H), 7.30 - 7.42 (m, 4 H), 7.47 (s, 1 H).

[0555]

Example 48

3-({[4-({1-[3-ethyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]-3-methylbutyl}amino)phenyl]carbonyl}amino)propanoic acid

[0556]



[0557]

(1) methyl 3-ethyl-1-(4-methoxyphenyl)-1H-pyrazole-4-carboxylate

Using methyl 3-oxopentanoate (3.3 g), dimethylformamide dimethylacetal (3.6 mL) and p-methoxyphenylhydrazine monohydrate (4.7 g) and in the same manner as in Example 15(1), the title object compound (6.0 g, 84%) was obtained as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.14 (t, J=7.5 Hz, 3 H), 2.92 (q, J=7.3 Hz, 2 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 7.00 (d, J=9.0 Hz, 2 H), 7.31 (d, J=9.0 Hz, 2 H), 7.99 (s, 1 H).

[0558]

(2)3-ethyl-1-(4-methoxyphenyl)-1H-pyrazole-4-carbaldehyde

Using methyl 3-ethyl-1-(4-methoxyphenyl)-1H-pyrazole-4-carboxylate (6.0 g) synthesized above and in the same manner as in Example 1(5), the title object compound (4.0 g, 76%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.18 (t, J=7.5 Hz, 3 H), 2.92 (q, J=7.5 Hz, 2 H), 3.88 (s, 3 H), 6.91 - 7.08 (m, 2 H), 7.12 - 7.22 (m, 2 H), 7.33 (d, J=9.0 Hz, 2 H), 8.03 (s, 1 H), 9.97 (s, 1 H).

[0559]

(3)1-[3-ethyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]-3-methylbutan-1-ol

Using 3-ethyl-1-(4-methoxyphenyl)-1H-pyrazole-4-carbaldehyde (2.1 g) synthesized above and in the same manner as in Example 1(6), the title object compound (1.2 g, 47%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 (6 H, d, J=6.4 Hz), 1.06 (3 H, t, J=7.6 Hz), 1.50 (1 H, d, J=4.3 Hz), 1.59 - 1.96 (3 H, m), 2.70 (2 H, q, J=7.5 Hz), 3.86 (3 H, s), 4.77 (1 H, dt, J=8.1, 5.1 Hz), 6.97 (2 H, d, J=8.9 Hz), 7.31 (2 H, d, J=8.9 Hz), 7.60 (1 H, s).

[0560]

(4) 3-({[4-({1-[3-ethyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]-3-methylbutyl}amino)phenyl]carbonyl}amino)propanoic acid

Using in 1-[3-ethyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]-3-methylbutan-1-ol (0.5 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.41 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.2 g, 25%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.20 (m, 9 H), 1.70 - 1.90 (m, 3 H), 2.63 (d, J=6.0 Hz, 4 H), 3.67 (d, J=5.5 Hz, 2 H), 3.84 (s, 3 H), 4.48 (t, J=6.8 Hz, 1 H), 6.58 (d, J=8.1 Hz, 2 H), 6.65 - 6.80 (m, 1 H), 6.95 (d, J=8.9 Hz, 2 H), 7.25 - 7.79

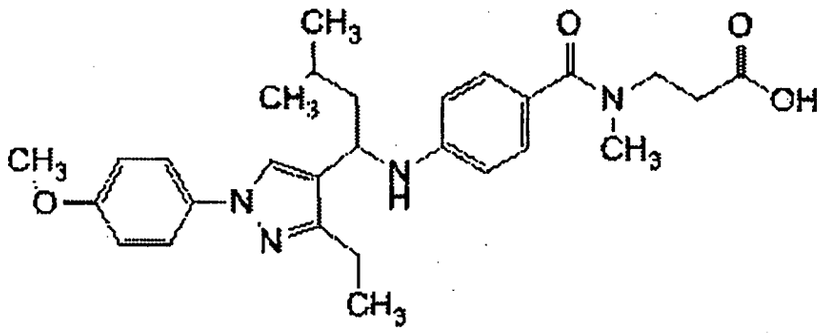
(m, 5 H).

[0561]

Example 49

3-[{[4-({1-[3-ethyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]-3-methylbutyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0562]



[0563]

Using 1-[3-ethyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]-3-methylbutan-1-ol (0.5 g) synthesized in Example 48(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.44 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.1 g, 12%) was obtained as a white solid.

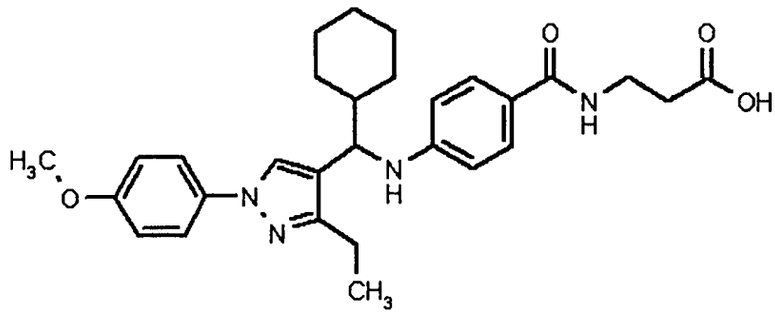
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 1.09 (m, 9 H), 1.70 - 1.80 (m, 3 H), 2.59 - 2.81 (m, 4 H), 3.11 (s, 3 H), 3.74 (t, J=6.5 Hz, 2 H), 3.86 (s, 3 H), 4.41 - 4.57 (m, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.97 (d, J=8.9 Hz, 2 H), 7.25 - 7.36 (m, 4 H), 7.53 (s, 1 H).

[0564]

Example 50

3-({[4-({cyclohexyl[3-ethyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0565]



[0566]

(1) cyclohexyl[3-ethyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methanol

Using 3-ethyl-1-(4-methoxyphenyl)-1H-pyrazole-4-carbaldehyde (2.1 g) synthesized in Example 48(2) and in the same manner as in Example 1(6), the title object compound (1.9 g, 65%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.82 - 2.18 (m., 12H), 2.66 (q, J=7.6 Hz, 2 H), 3.86 (s, 3 H), 4.34 (dd, J=8.2, 3.7 Hz, 1 H), 6.97 (d, J=9.0 Hz, 2 H), 7.32 (d, J=9.0 Hz, 2 H), 7.57 (s, 1 H).

[0567]

(2) 3-({[4-({cyclohexyl[3-ethyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

Using cyclohexyl[3-ethyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methanol (0.5 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.38 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.35 mg, 43%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 (t, J=7.5 Hz, 3 H), 1.02 - 2.07 (m, 11 H), 2.64 (t, J=7.3 Hz, 4 H), 3.58 - 3.74 (m, 2 H), 3.84 (s, 3 H), 4.20 (d, J=7.0 Hz, 1 H), 6.54 (d, J=8.7 Hz, 2 H), 6.61 - 6.72 (m, 1 H), 6.95 (d, J=9.0 Hz, 2 H), 7.25 - 7.55 (m, 5 H).

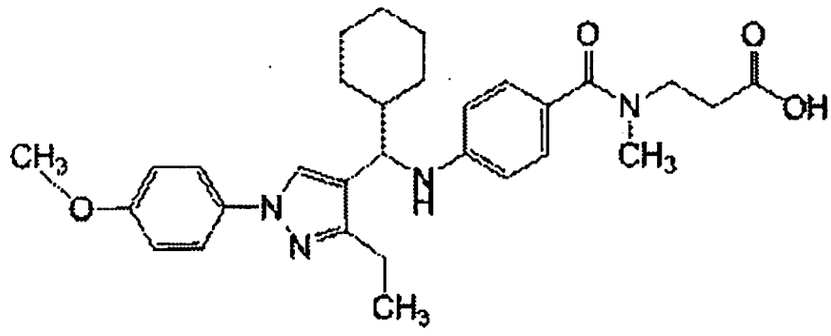
[0568]

Example 51

3-[{[4-({cyclohexyl[3-ethyl-1-(4-methoxyphenyl)-1H-pyrazol-4-

yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0569]



[0570]

Using cyclohexyl[3-ethyl-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]methanol (0.5 g) synthesized in Example 50(1) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.40 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.15 mg, 18%) was obtained as a white solid.

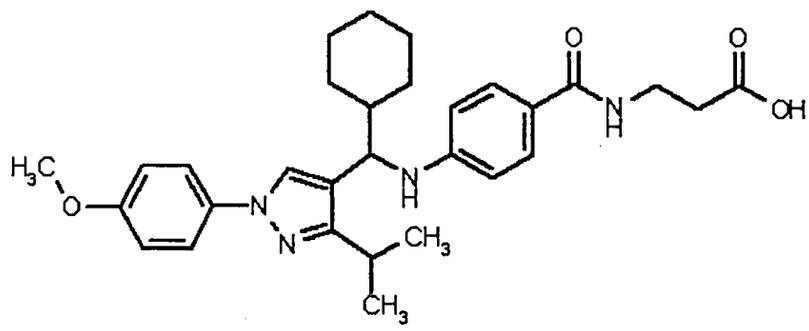
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 (t, J=7.5 Hz, 3 H), 1.01 - 2.11 (m, 12 H), 2.56 - 2.83 (m, 4 H), 3.09 (s, 3 H), 3.73 (t, J=6.4 Hz, 2 H), 3.85 (s, 3 H), 4.19 (d, J=6.8 Hz, 1 H), 6.54 (d, J=8.7 Hz, 2 H), 6.96 (d, J=8.9 Hz, 2 H), 7.27 - 7.37 (m, 4 H), 7.48 (s, 1 H).

[0571]

Example 52

3-({[4-({cyclohexyl[1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0572]



[0573]

(1) methyl 1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazole-4-carboxylate

Using methyl 4-methyl-3-oxopentanoate (3.6 g), dimethylformamide dimethylacetal (3.5 mL) and p-methoxyphenylhydrazine monohydrochloride (4.5 g) and in the same manner as in Example 15(1), the title object compound (3.5 g, 51%) was obtained as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.37 (d, J=6.0 Hz, 6 H), 3.20 - 3.40 (m, 1 H), 3.86 (s, 3 H), 3.90 (s, 3 H), 6.98 (d, J=9.0 Hz, 2 H), 7.27 (d, J=9.0 Hz, 2 H), 7.29 (s, 1 H), 7.99 (s, 1 H).

[0574]

(2) 1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazole-4-carbaldehyde

Using methyl 1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazole-4-carboxylate (3.5 g) synthesized above and in the same manner as in Example 1(5), the title object compound (2.6 g, 84%) was obtained as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.37 (d, J=7.0 Hz, 6 H), 3.12 - 3.25 (m, 1 H), 3.88 (s, 3 H), 7.01 (d, J=9.0 Hz, 2 H), 7.29 (d, J=9.0 Hz, 2 H), 8.05 (s, 1 H), 10.06 (s, 1 H).

[0575]

(3) cyclohexyl[1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]methanol

Using 1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazole-4-carbaldehyde (1.3 g) synthesized above and in the same manner as in Example 1(6), the title object compound (1.4 g, 84%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.81 - 2.21 (m., 18 H), 3.08 (quint, J=7.2 Hz, 1 H), 3.86 (s, 3 H), 4.52 (dd, J=8.7, 3.8 Hz, 1 H), 6.96 (d, J=9.0 Hz, 2 H), 7.27 (d, J=9.0 Hz, 2 H), 7.59 (s, 1 H).

[0576]

(4) 3-({[4-({cyclohexyl[1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic

acid

Using cyclohexyl[1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]methanol (0.70 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.52 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.34 g, 30%) was obtained as a white solid.

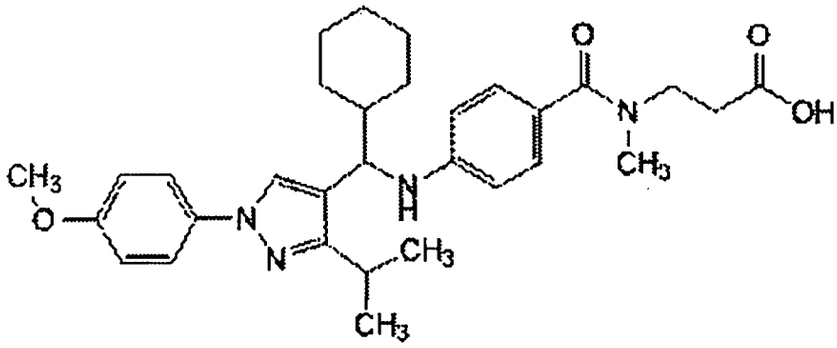
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.10 (d, J=7.2 Hz, 3 H), 1.18 (d, J=7.2 Hz, 3 H), 1.20 - 2.06 (m, 12 H), 2.64 (t, J=5.5 Hz, 2 H), 3.10 (quint, J=7.3 Hz, 1 H), 3.66 (q, J=5.8 Hz, 2 H), 3.85 (s, 3 H), 4.37 (d, J=7.2 Hz, 1 H), 6.57 (d, J=8.7 Hz, 2 H), 6.61 - 6.74 (m, 1 H), 6.94 (d, J=8.7 Hz, 2 H), 7.20 - 7.58 (m, 5 H).

[0577]

Example 53

3-[{[4-({cyclohexyl[1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0578]



[0579]

Using cyclohexyl[1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]methanol (0.70 g) synthesized in Example 52(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.55 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.28 g, 24%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.11 (d, J=6.8 Hz, 3 H), 1.19 (d, J=7.2 Hz, 3 H), 1.20 - 2.13 (m, 11 H), 2.72 (t, J=6.1 Hz, 2 H),

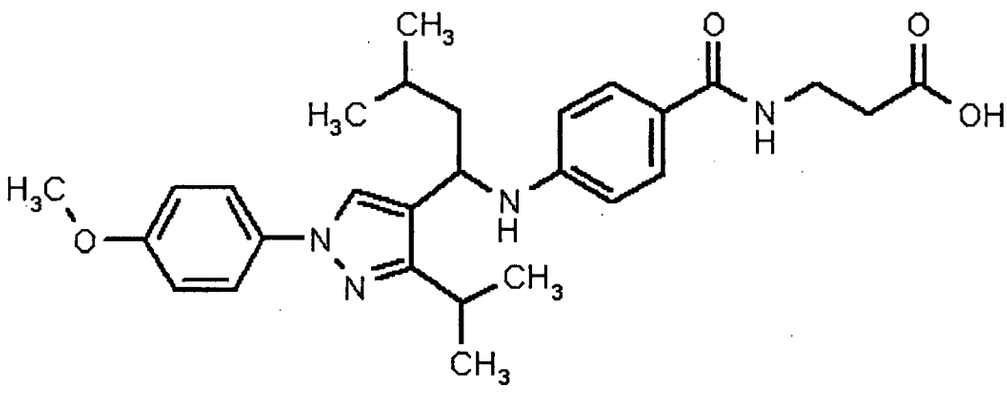
3.03 - 3.23 (m, 4 H), 3.73 (t, J=6.6 Hz, 2 H), 3.85 (s, 3 H), 4.36 (d, J=7.2 Hz, 1 H), 6.55 (d, J=8.3 Hz, 2 H), 6.95 (d, J=9.1 Hz, 2 H), 7.21 - 7.35 (m, 4 H), 7.50 (s, 1 H).

[0580]

Example 54

3-({[4-({1-[1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]-3-methylbutyl}amino)phenyl]carbonyl}amino)propanoic acid

[0581]



[0582]

(1) 1-[1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]-3-methylbutan-1-ol

Using 1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazole-4-carbaldehyde (1.3 g) synthesized in Example 52(2) and in the same manner as in Example 1(6), the title object compound (1.6 g, 98%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.99 (d, J=5.7 Hz, 6 H), 1.28 (dd, J=17.0, 7.2 Hz, 6 H), 1.75 - 1.98 (m, 2 H), 2.99 - 3.19 (m, 1 H), 3.86 (s, 3 H), 4.96 (dd, J=8.4, 4.4 Hz, 1 H), 6.97 (d, J=8.9 Hz, 2 H), 7.26 (d, J=9.0 Hz, 2 H), 7.62 (s, 1 H).

[0583]

(2) 3-({[4-({1-[1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]-3-methylbutyl}amino)phenyl]carbonyl}amino)propanoic acid

Using 1-[1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]-3-methylbutan-1-ol (0.57 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.45

g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (28.0 mg, 3%) was obtained as a white solid.

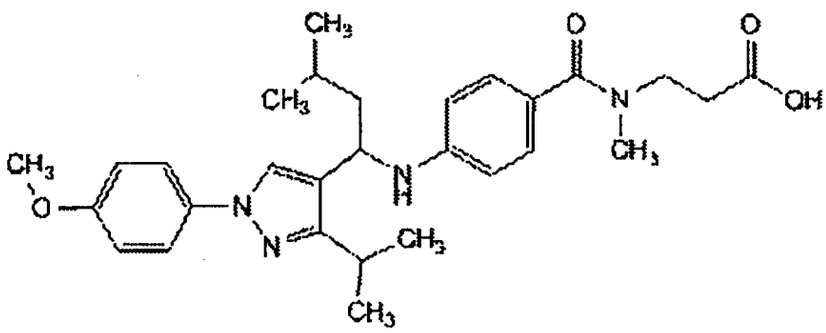
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 (d, J=6.4 Hz, 3 H), 1.02 (d, J=6.4 Hz, 3 H), 1.11 - 1.98 (m, 9 H), 2.67 (t, J=5.7 Hz, 2 H), 2.98 - 3.19 (m, 1 H), 3.68 (t, J=6.0 Hz, 2 H), 3.85 (s, 3 H), 4.66 (d, J=9.0 Hz, 1 H), 6.51 - 6.77 (m, 3 H), 6.95 (d, J=8.9 Hz, 2 H), 7.26 - 7.59 (m, 5 H).

[0584]

Example 55

3-[{[4-({1-[1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]-3-methylbutyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0585]



[0586]

Using 1-[1-(4-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]-3-methylbutan-1-ol (0.57 g) synthesized in Example 54(1) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.48 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (8.0 mg, 1%) was obtained as a white solid.

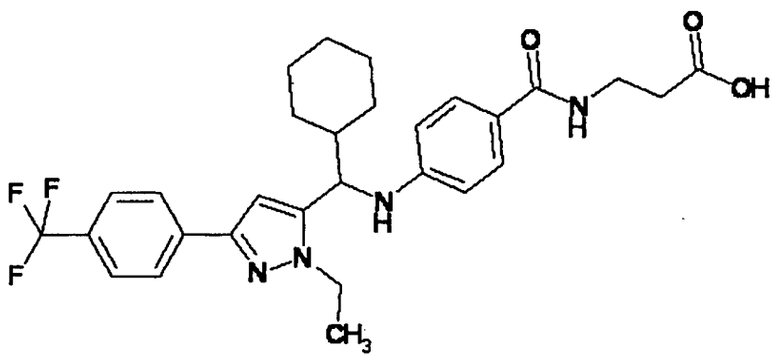
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 (d, J=6.6 Hz, 3 H), 1.02 (d, J=6.4 Hz, 3 H), 1.11 - 2.01 (m, 9 H), 2.72 (br. s., J=6.0 Hz, 2 H), 2.96 - 3.24 (m, 4 H), 3.74 (br. s., J=6.0 Hz, 2 H), 3.86 (s, 3 H), 4.63 (d, J=6.0 Hz, 1 H), 6.50 - 6.70 (m, 2 H), 6.96 (d, J=8.9 Hz, 2 H), 7.21 - 7.38 (m, 4 H), 7.59 (br. s., 1 H).

[0587]

Example 56

3-[({4-[(cyclohexyl{1-ethyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrazol-5-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[0588]



[0589]

(1) ethyl 1-ethyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrazole-5-carboxylate

1-[4-(Trifluoromethyl)phenyl]ethanone (12.0 g) was dissolved in ethanol (100 mL), sodium hydride (60%, oily, 2.8 g) was carefully added under ice-cooling. After stirring for 5 min, diethyl oxalate (8.7 mL) was added, and the mixture was stirred at room temperature overnight. The precipitate (18.6 g) was collected, and to 7.3 g thereof were added ethanol (16 mL), 6N hydrochloric acid (4.3 mL) and ethylhydrazine (1.6 g), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (5.7 g, 78%) as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.42 (t, J=7.2 Hz, 3 H), 1.50 (t, J=7.2 Hz, 3 H), 4.39 (q, J=7.2 Hz, 2 H), 4.66 (q, J=7.2 Hz, 2 H), 7.17 (s, 1 H), 7.65 (d, J=8.1 Hz, 2 H), 7.92 (d, J=8.1 Hz, 2 H).

[0590]

(2) 1-ethyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrazole-5-carbaldehyde

Using ethyl 1-ethyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrazole-5-carboxylate (5.7 g) synthesized above and in the same manner as in Example 1(5), the title object compound (3.2 g, 68%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.48 (t, J=7.2 Hz, 3 H), 4.25 (q, J=7.2 Hz, 2 H), 6.85 (s, 1 H), 7.54 (d, J=8.0 Hz, 2 H), 7.77 (d, J=8.0 Hz, 2 H), 10.01 (s, 1 H).

(3) cyclohexyl{1-ethyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrazol-5-yl}methanol

Using 1-ethyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrazole-5-carbaldehyde (2.28 g) synthesized above and in the same manner as in Example 1(6), the title object compound (1.2 g, 41%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 2.00 (m, 11 H), 1.39 (t, J=7.2 Hz, 3 H), 2.27 (d, J=4.7 Hz, 1 H), 4.00 - 4.25 (m, 2 H), 4.53 (dd, J=6.4, 4.7 Hz, 1 H), 6.23 (s, 1 H), 7.53 (d, J=7.9 Hz, 2 H), 7.72 (d, J=7.9 Hz, 2 H).

[0591]

(4) 3-[({4-[(cyclohexyl{1-ethyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrazol-5-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

Using cyclohexyl{1-ethyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrazol-5-yl}methanol (0.6 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.42 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.18 g, 20%) was obtained as a white solid.

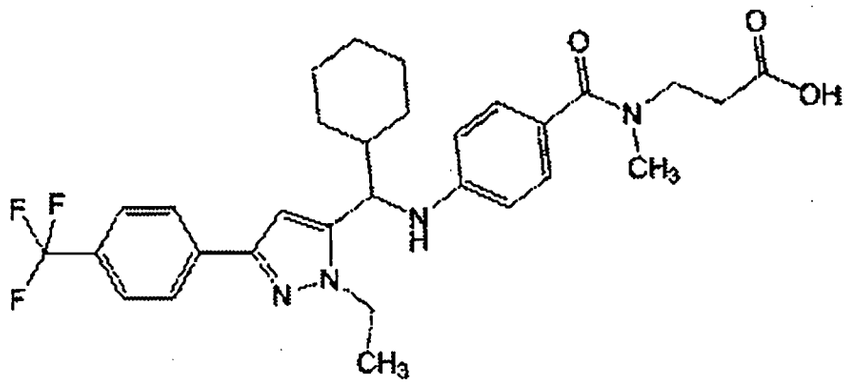
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 - 1.27 (m, 11 H), 1.33 (t, J=7.3 Hz, 3 H), 2.68 (t, J=5.5 Hz, 2 H), 3.59 - 3.80 (m, 2 H), 4.11 (q, J=7.2 Hz, 2 H), 4.39 (d, J=6.8 Hz, 1 H), 6.16 (s, 1 H), 6.64 (d, J=8.7 Hz, 2 H), 6.70 - 6.83 (m, 1 H), 7.48 (d, J=8.1 Hz, 2 H), 7.58 (d, J=8.7 Hz, 2 H), 7.69 (d, J=8.1 Hz, 2 H).

[0592]

Example 57

3-[({4-[(cyclohexyl{1-ethyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrazol-5-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0593]



[0594]

Using cyclohexyl{1-ethyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrazol-5-yl}methanol (0.6 g) synthesized in Example 56(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.48 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.19 g, 19%) was obtained as a white solid.

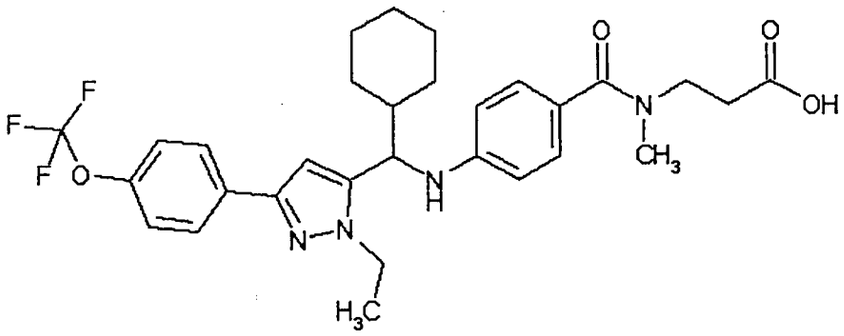
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 2.00 (m, 11 H), 1.35 (t, J=7.2 Hz, 3 H), 2.62 - 2.78 (m, 2 H), 3.09 (s, 3 H), 3.75 (t, J=6.6 Hz, 2 H), 4.15 (q, J=7.2 Hz, 2 H), 4.39 (d, J=6.6 Hz, 1 H), 6.18 (s, 1 H), 6.61 (d, J=8.7 Hz, 2 H), 7.25 (d, J=8.7 Hz, 2 H), 7.50 (d, J=8.1 Hz, 2 H), 7.70 (d, J=8.1 Hz, 2 H).

[0595]

Example 58

3-[({4-[(cyclohexyl{1-ethyl-3-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-5-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0596]



[0597]

(1) ethyl 1-ethyl-3-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-5-carboxylate

Using 1-[4-(trifluoromethoxy)phenyl]ethanone (13.0 g), sodium hydride (60%, oily, 2.8 g), diethyl oxalate (8.7 mL) and ethylhydrazine (4.2 g) and in the same manner as in Example 56(1), the title object compound (19.4 g, 92%) was obtained as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.34 - 1.53 (m, 6 H), 4.24 (d, J=7.2 Hz, 2 H), 4.23 (q, J=7.2 Hz, 2 H), 4.43 (q, J=7.2 Hz, 2 H), 4.45 (d, J=7.2 Hz, 2 H), 6.82 (s, 1 H), 7.33 (d, J=9.0 Hz, 2 H), 7.44 (d, J=9.0 Hz, 2 H).

[0598]

(2) 1-ethyl-3-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-5-carbaldehyde

Using ethyl 1-ethyl-3-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-5-carboxylate (5.0 g) synthesized above and in the same manner as in Example 1(5), the title object compound (4.9 g, 38%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.48 (t, J=7.3 Hz, 3 H), 4.23 (q, J=7.3 Hz, 2 H), 6.80 (s, 1 H), 7.30 - 7.58 (m, 4 H), 10.00 (s, 1 H).

[0599]

(3) cyclohexyl{1-ethyl-3-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-5-yl}methanol

Using 1-ethyl-3-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-5-carbaldehyde (2.5 g) synthesized above and in the same

manner as in Example 1(6), the title object compound (1.7 g, 54%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.26 -2.00 (m, 11 H), 1.39 (t, J=7.2 Hz, 3 H), 4.12 (d, J=7.2 Hz, 2 H), 4.52 (d, J=6.4 Hz, 1 H), 6.18 (s, 1 H), 7.30 (d, J=8.7 Hz, 2 H), 7.43 (d, J=8.7 Hz, 2 H).

[0600]

(4) 3-[({4-[(cyclohexyl{1-ethyl-3-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-5-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

Using cyclohexyl{1-ethyl-3-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-5-yl}methanol (0.39 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.32 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.06 g, 11%) was obtained as a white solid.

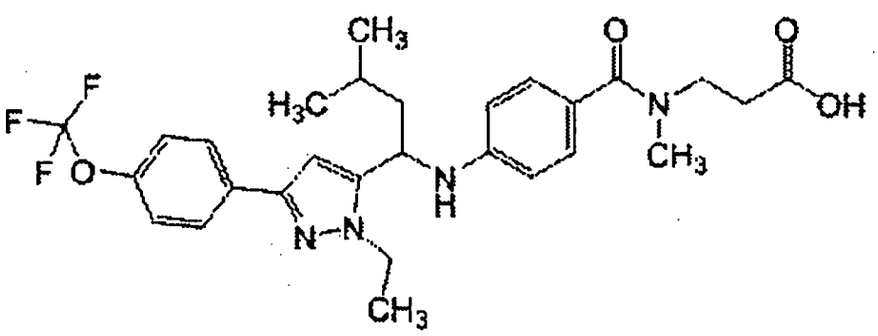
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.99 - 2.00 (m, 11 H), 1.36 (t, J=7.2 Hz, 3 H), 2.74 (t, J=6.2 Hz, 2 H), 3.10 (s, 3 H), 3.74 (t, J=6.2 Hz, 2 H), 4.12 (q, J=7.2 Hz, 2 H), 4.37 (d, J=6.4 Hz, 1 H), 6.10 (s, 1 H), 6.63 (d, J=8.7 Hz, 2 H), 7.26 - 7.46 (m, 6 H).

[0601]

Example 59

3-[({4-[(1-{1-ethyl-3-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-5-yl}-3-methylbutyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0602]




[0603]

(1) 1-{1-ethyl-3-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-5-yl}-3-methylbutan-1-ol

1-Ethyl-3-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-5-carbaldehyde (2.5 g) synthesized in Example 58(2) was dissolved in tetrahydrofuran (20 mL), and 1M isobutylmagnesium bromide tetrahydrofuran solution (12 mL) was added dropwise at 0°C. In the same manner as in Example 1(6), the title object compound (0.9 g, 31%) was obtained as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 (d, J=6.4 Hz, 6 H), 1.39 (t, J=7.2 Hz, 3 H), 1.56 - 1.98 (m, 3 H), 2.21 (d, J=4.3 Hz, 1 H), 4.10 - 4.30 (q, J=7.2 Hz, 2 H), 4.86 (ddd, J=8.9, 4.7, 4.3 Hz, 1 H), 6.22 (s, 1 H), 7.32 - 7.50 (m, 4 H).

[0604]

(2) 3-[({4-[(1-{1-ethyl-3-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-5-yl}-3-methylbutyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

Using cyclohexyl1-{1-ethyl-3-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-5-yl}-3-methylbutan-1-ol (0.39 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.28 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.02 g, 4%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 (dd, J=19.1, 6.2 Hz, 6 H), 1.34 (t, J=7.2 Hz, 3 H), 1.55 - 1.97 (m, 3 H), 2.70 (br. s., 2 H), 3.07 (s, 3 H), 3.73 (br. s., 2 H), 4.10 (q, J=7.2 Hz, 2 H), 4.61 (t, J=6.8 Hz, 1 H), 6.17 (s, 1 H), 6.67 (d, J=8.0 Hz, 2 H), 7.34 - 7.49 (m, 6 H).

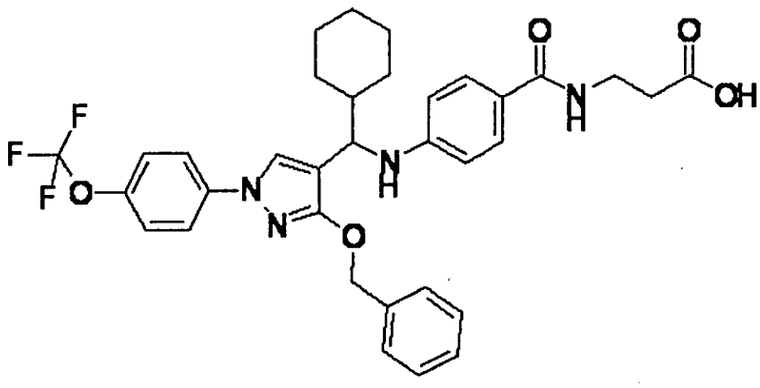
[0605]

Example 60

3-{[(4-{[{3-(benzyloxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0606]

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[0607]

(1) 3-(benzyloxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carbaldehyde

Using ethyl 3-(benzyloxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carboxylate (3.1 g) synthesized in the method described in EP1394154 and in the same manner as in Example 1(5), the title object compound (2.1 g, 75%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 5.50 (s, 2 H), 7.27 - 7.70 (m, 9 H), 8.24 (s, 1 H), 10.00 (s, 1 H).

[0608]

(2) {3-(benzyloxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}(cyclohexyl)methanol

Using 3-(benzyloxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carbaldehyde (2.1 g) synthesized above and in the same manner as in Example 1(6), the title object compound (1.9 g, 76%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 2.00 (m, 12 H), 4.44 (dd, J=6.8, 5.3 Hz, 1 H), 5.36 (s, 2 H), 7.26 - 7.51 (m, 9 H), 7.66 (s, 1 H).

[0609]

(3) 3-{[(4-{[{3-(benzyloxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

Using {3-(benzyloxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}(cyclohexyl)methanol (0.50 g) synthesized above

and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.26 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.39 g, 56%) was obtained as a white solid.

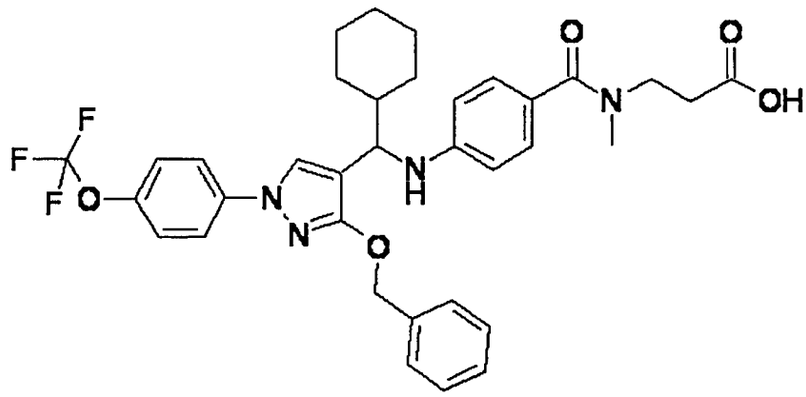
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.78 - 2.00 (m, 11 H), 2.12 - 2.42 (m, 2 H), 3.30 - 3.57 (m, 2 H), 4.14 (d, J=7.0 Hz, 1 H), 5.31 (s, 2 H), 6.41 (d, J=8.5 Hz, 2 H), 6.77 (br. s., 1 H), 7.12 (d, J=9.0 Hz, 2 H), 7.29 - 7.67 (m, 10 H).

[0610]

Example 61

3-{[(4-{[{3-(benzyloxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[0611]



[0612]

Using {3-(benzyloxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}(cyclohexyl)methanol (0.50 g) synthesized in Example 60(2) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.28 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.37 g, 52%) was obtained as a white solid.

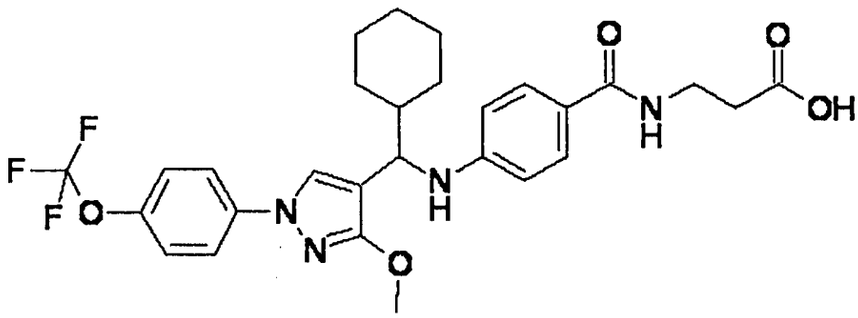
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.87 - 2.05 (m, 11 H), 2.52 (t, J=6.0 Hz, 2 H), 2.96 (s, 3 H), 3.50 - 3.78 (m, 2 H), 4.20 (d, J=6.8 Hz, 1 H), 5.25 - 5.46 (m, 2 H), 6.47 (d, J=8.7 Hz, 2 H), 7.12 - 7.62 (m, 12 H).

[0613]

Example 62

3-[({4-[(cyclohexyl{3-methoxy-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[0614]



[0615]

(1) 3-methoxy-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carbaldehyde

Using ethyl 3-methoxy-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carboxylate (4.8 g) synthesized in the method described in WO2007/89031 and in the same manner as in Example 1(5), the title object compound (1.0 g, 35%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 4.10 (s, 3 H), 7.33 (d, J=9.1 Hz, 2 H), 7.69 (d, J=9.1 Hz, 2 H), 8.23 (s, 1 H), 9.87 (s, 1 H).

(2) cyclohexyl{3-methoxy-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methanol

Using 3-methoxy-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carbaldehyde (1.0 g) synthesized above and in the same manner as in Example 1(6), the title object compound (1.5 g, 75%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 2.02 (m, 11 H), 3.62 (br. s., 1 H), 4.00 (s, 3 H), 4.40 (dd, J=7.0, 4.7 Hz, 1 H), 7.24 - 7.62 (m, 4 H), 7.64 (s, 1 H).

[0616]

(3) ethyl 3-methoxy-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carboxylate

Using cyclohexyl{3-methoxy-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methanol (0.75 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.47 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.10 g, 9%) was obtained as a white solid.

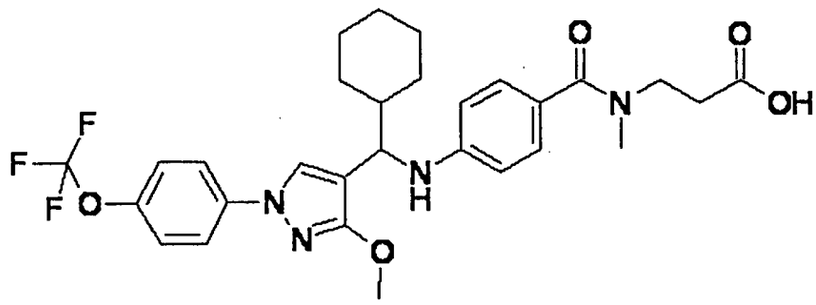
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.88 - 2.00 (m, 11 H), 2.58 (t., J=6.0 Hz, 2 H), 3.54 - 3.68 (m, 2 H), 4.00 (s, 3 H), 4.20 (d, J=6.6 Hz, 1 H), 6.52 (d, J=8.7 Hz, 2 H), 6.56 - 6.68 (m, 1 H), 7.20 (d, J=8.3 Hz, 2 H), 7.48 - 7.59 (m, 5 H).

[0617]

Example 63

3-[({4-[(cyclohexyl{3-methoxy-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0618]



[0619]

Using cyclohexyl{3-methoxy-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methanol (0.75 g) synthesized in Example 62(2) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.50 g) synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.13 g, 12%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 2.02 (m, 11 H), 2.68 (t, J=6.2 Hz, 2 H), 3.05 (s, 3 H), 3.71 (t, J=6.4 Hz, 2 H), 4.01 (s, 3 H), 4.19 (d, J=6.6 Hz, 1 H), 6.53 (d, J=8.7 Hz, 2 H),

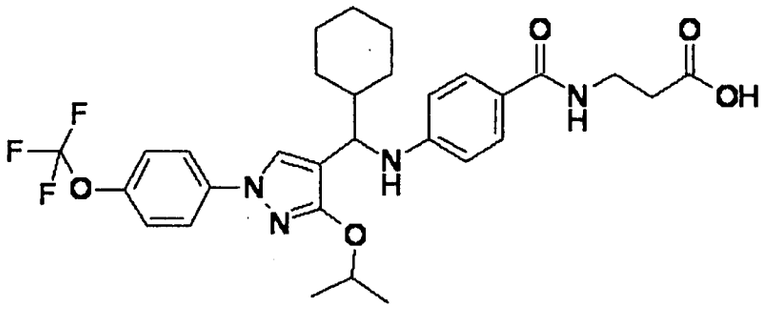
7.17 - 7.28 (m, 4 H), 7.47 - 7.61 (m, 3 H).

[0620]

Example 64

3-[({4-[(cyclohexyl{3-(1-methylethoxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[0621]



[0622]

(1) 3-(1-methylethoxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carbaldehyde

Using ethyl 3-(1-methylethoxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carboxylate (1.3 g) synthesized in the method described in WO2007/89031 and in the same manner as in Example 1(5), the title object compound (0.43 g, 37%) was obtained as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.33 (d, J=6.2 Hz, 6 H), 5.20 (quint, J=6.2 Hz, 1 H), 7.03 - 7.76 (m, 4 H), 7.98 (s, 1 H), 9.78 (s, 1 H).

[0623]

(2) cyclohexyl{3-(1-methylethoxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methanol

Using 3-(1-methylethoxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazole-4-carbaldehyde (0.43 g) synthesized above and in the same manner as in Example 1(6), the title object compound (0.40 g, 74%) was obtained as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.47 - 2.20 (m, 17 H), 3.61 (br, s. 1 H), 4.20 - 4.40 (m, 2 H), 7.28 (d, J=8.7 Hz, 2 H), 7.57 (s, 1 H), 7.74 (d, J=8.7 Hz, 2 H).

[0624]

(3) 3-[({4-[(cyclohexyl{3-(1-methylethoxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

Using cyclohexyl{3-(1-methylethoxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methanol (0.20 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.12 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.11 g, 36%) was obtained as a white solid.

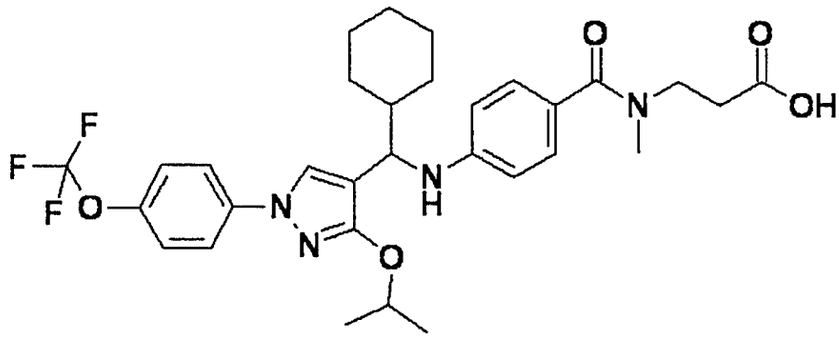
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 2.08 (m, 11 H), 1.11 - 1.18 (m, 6 H), 2.50 - 2.66 (m, 2 H), 3.54 - 3.70 (m, 2 H), 4.11 - 4.30 (m, 2 H), 6.57 (d, J=8.7 Hz, 2 H), 6.69 (br. s., 1 H), 7.26 (d, J=8.7 Hz, 2 H), 7.46 (s, 1 H), 7.57 (d, J=8.7 Hz, 2 H).

[0625]

Example 65

3-[({4-[(cyclohexyl{3-(1-methylethoxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0626]




[0627]

Using cyclohexyl{3-(1-methylethoxy)-1-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}methanol (0.20 g) synthesized in Example 64(2) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.13 g)

synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.11 g, 36%) was obtained as a white solid.

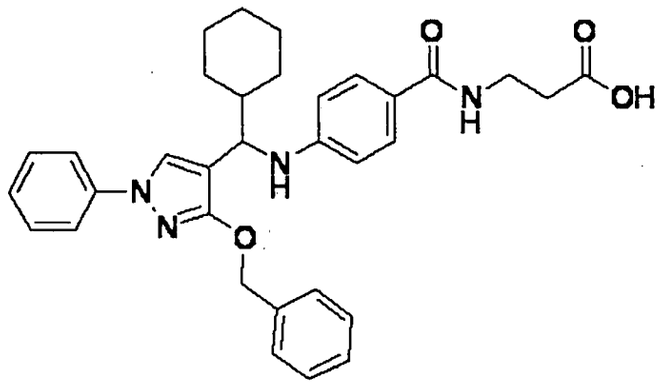
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 - 2.00 (m, 11 H), 1.12 - 1.19 (m, 6 H), 2.53 - 2.70 (m, 2 H), 3.05 (s, 3 H), 3.63 - 3.78 (m, 2 H), 4.13 - 4.29 (m, 2 H), 6.57 (d, J=8.9 Hz, 2 H), 7.27 - 7.32 (m, 4 H), 7.46 (s, 1 H), 7.72 (d, J=8.9 Hz, 2 H).

[0628]

Example 66

3-({[4-({[3-(benzyloxy)-1-phenyl-1H-pyrazol-4-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0629]



[0630]

(1) 3-(benzyloxy)-1-phenyl-1H-pyrazole-4-carbaldehyde

Using ethyl 3-(benzyloxy)-1-phenyl-1H-pyrazole-4-carboxylate (1.8 g) synthesized in the method described in EP1394154 and in the same manner as in Example 1(5), the title object compound (1.4 g, 90%) was obtained as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 5.50 (s, 2 H), 7.29 - 7.78 (m, 10 H), 8.26 (s, 1 H), 9.98 (s, 1 H).

[0631]

(2) [3-(benzyloxy)-1-phenyl-1H-pyrazol-4-yl](cyclohexyl)methanol

Using 3-(benzyloxy)-1-phenyl-1H-pyrazole-4-carbaldehyde (1.4 g) synthesized above and in the same manner as in Example 1(6), the title object compound (1.6 g, 91%) was obtained as

an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.58 - 2.20 (m, 12 H), 4.44 (dd, J=7.2, 5.3 Hz, 1 H), 5.37 (s, 2 H), 7.10 - 7.62 (m, 10 H), 7.69 (s, 1 H).

[0632]

(3) 3-({[4-({[3-(benzyloxy)-1-phenyl-1H-pyrazol-4-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}amino)propanoic acid

Using [3-(benzyloxy)-1-phenyl-1H-pyrazol-4-yl](cyclohexyl)methanol (0.79 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.51 g) synthesized in Example 1(2) and in the same manner as in Example 1(7), the title object compound (0.51 g, 43%) was obtained as a white solid.

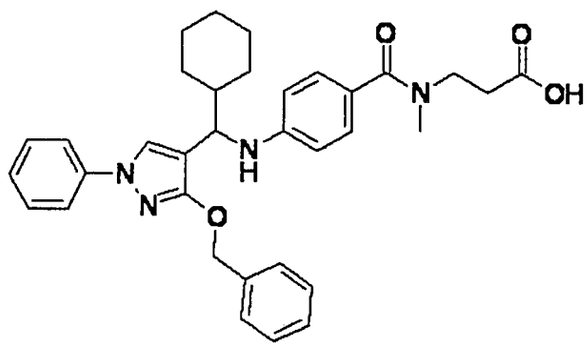
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 - 1.97 (m, 11 H), 2.30 - 2.48 (m, 2 H), 3.37 - 3.58 (m, 2 H), 4.18 (d, J=6.6 Hz, 1 H), 5.24 - 5.42 (m, 2 H), 6.44 (d, J=8.7 Hz, 2 H), 6.66 (br. s., 1 H), 7.02 - 7.63 (m, 13 H).

[0633]

Example 67

3-[{[4-({[3-(benzyloxy)-1-phenyl-1H-pyrazol-4-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoic acid

[0634]




[0635]

Using [3-(benzyloxy)-1-phenyl-1H-pyrazol-4-yl](cyclohexyl)methanol (0.79 g) synthesized in Example 66(2)

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and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate synthesized in Example 2(2) and in the same manner as in Example 1(7), the title object compound (0.68 g, 55%) was obtained as a white solid.

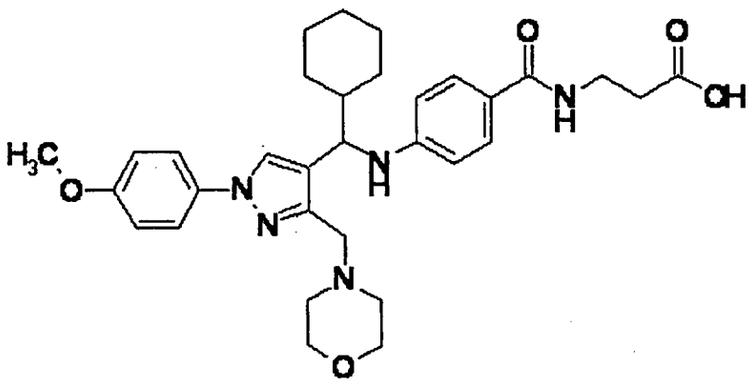
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 - 2.01 (m, 11 H), 2.71 (d, J=6.0 Hz, 1 H), 3.06 (s, 3 H), 3.71 (t, J=6.4 Hz, 2 H), 4.23 (d, J=6.6 Hz, 1 H), 5.28 - 5.47 (m, 2 H), 6.50 (d, J=8.7 Hz, 2 H), 7.10 - 7.64 (m, 13 H).

[0636]

Example 68

3-({[4-({cyclohexyl[1-(4-methoxyphenyl)-3-(morpholin-4-ylmethyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0637]



[0638]

(1) methyl 4-(morpholin-4-yl)-3-oxobutanoate

To a solution (300 mL) of methyl 4-chloro-3-oxobutanoate (27.1 g) in tetrahydrofuran was added morpholine (34.5 g) under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure, 1N hydrochloric acid (100 mL) was added, and the mixture was extracted with diethyl ether. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:10, volume ratio) to give the title

object compound (12.8 g, 35%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.37 - 2.55 (m, 4 H), 3.26 (s, 2 H), 3.52 (s, 2 H), 3.70 - 3.76 (m, 4 H), 3.74 (s, 3 H).

[0639]

(2) methyl 1-(4-methoxyphenyl)-3-(morpholin-4-ylmethyl)-1H-pyrazole-4-carboxylate

To methyl 4-(morpholin-4-yl)-3-oxobutanoate (7.0 g) - mentioned (1) was added dimethylformamide-dimethylacetal (4.9 mL), and the mixture was stirred at 100°C for 2 hr. The reaction mixture was allowed to cool to room temperature, ethanol (200 mL) and 4-methoxyphenylhydrazine hydrochloride (6.3 g) were added, and the mixture was stirred at 100°C for 3 hr. The mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. Water was added to the residue and the mixture was extracted with ethyl acetate. The extract was concentrated, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (10.6 g, 93%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.44 - 2.50 (m, 4 H), 3.60 - 3.65 (m, 4 H), 3.75 (s, 2 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 6.97 (d, J=9.1 Hz, 2 H), 7.68 (d, J=9.1 Hz, 2 H), 8.03 (s, 1 H).

[0640]

(3) 1-(4-methoxyphenyl)-3-(morpholin-4-ylmethyl)-1H-pyrazole-4-carbaldehyde

A solution (20 mL) of methyl 1-(4-methoxyphenyl)-3-(morpholin-4-ylmethyl)-1H-pyrazole-4-carboxylate (11.3 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added to an ice-cooled solution (80 mL) of lithium aluminum hydride (1.4 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr. The mixture was ice-cooled again, and water (3.7 mL), 1N aqueous sodium hydroxide solution (18.5 mL) and water (3.7 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was

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concentrated under reduced pressure to give a crude product (8.5 g) of 1-(4-methoxyphenyl)-3-(morpholin-4-ylmethyl)-1H-pyrazole-4-methanol as a pale-yellow oil. This was dissolved in toluene (150 mL), manganese dioxide (15 g) was added, and the mixture was heated for 30 min with a Dean-Stark trap. The reaction mixture was allowed to cool to room temperature, and manganese dioxide was collected by filtration. The solvent was evaporated under reduced pressure to give the title object compound (7.2 g, 70%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.44 - 2.50 (m, 4 H), 3.60 - 3.65 (m, 4 H), 3.72 (s, 2 H), 3.88 (s, 3 H), 6.99 (d, J=9.1 Hz, 2 H), 7.60 (d, J=9.1 Hz, 2 H), 8.08 (s, 1 H), 10.10 (s, 1 H).

[0641]

(4) cyclohexyl[1-(4-methoxyphenyl)-3-(morpholin-4-ylmethyl)-1H-pyrazol-4-yl]methanol

To a solution (15 mL) of 1-(4-methoxyphenyl)-3-(morpholin-4-ylmethyl)-1H-pyrazole-4-carbaldehyde (2.0 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added dropwise cyclohexylmagnesium bromide (10 mL, 1M tetrahydrofuran solution) under ice-cooling. After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (1.3 g, 51%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 2.20 (m, 11 H), 2.24 - 2.50 (m, 4 H), 3.47 (d, J=12.0 Hz, 1 H), 3.58 - 3.73 (m, 5 H), 3.87 (s, 3 H), 4.43 (d, J=6.6 Hz, 1 H), 6.10 (s, 1 H), 6.98 (d, J=8.9 Hz, 2 H), 7.26 (d, J=8.9 Hz, 2 H), 7.49 (s, 1 H).

[0642]

(5)3-({[4-({cyclohexyl[1-(4-methoxyphenyl)-3-(morpholin-4-ylmethyl)-1H-pyrazol-4-

yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

To a solution (15 mL) of cyclohexyl[1-(4-methoxyphenyl)-3-(morpholin-4-ylmethyl)-1H-pyrazol-4-yl]methanol (0.65 g) synthesized in the above-mentioned (4) in tetrahydrofuran was added thionyl chloride (0.37 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (15 mL) was carefully poured. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (15 mL), sodium iodide (0.37 g), sodium carbonate (0.27 g) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.39 g) synthesized in Example 1(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-({[4-({cyclohexyl[1-(4-methoxyphenyl)-3-(morpholin-4-ylmethyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoate (0.35 g) as a pale-yellow oil. This was dissolved in ethanol (2 mL), 1N aqueous sodium hydroxide solution (1.5 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.5 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.22 g, 22%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 2.00 (m, 11 H), 2.24 - 2.50 (m, 4 H), 2.66 (br s., 2 H), 3.44 (s, 2 H), 3.58 - 3.73 (m, 6 H), 3.85 (s, 3 H), 4.47 (d, J=7.2 Hz, 1 H), 6.47 - 6.79 (m, 3 H), 6.94 (d, J=8.7 Hz, 2 H), 7.26 - 7.30 (m, 2 H), 7.50

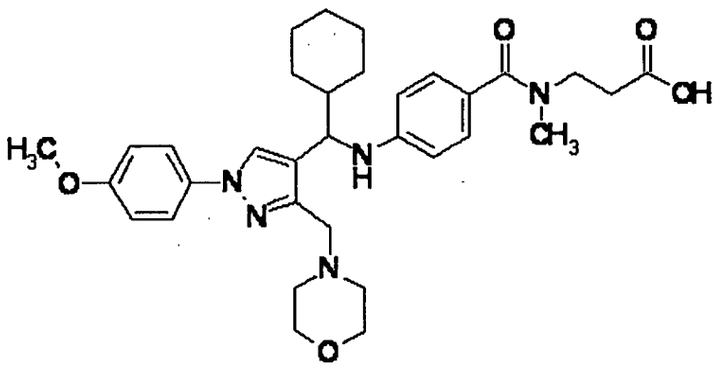
- 7.60 (m, 3 H).

[0643]

Example 69

3-[{[4-({cyclohexyl[1-(4-methoxyphenyl)-3-(morpholin-4-ylmethyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0644]



[0645]

To a solution (15 mL) of cyclohexyl[1-(4-methoxyphenyl)-3-(morpholin-4-ylmethyl)-1H-pyrazol-4-yl]methanol (0.65 g) synthesized in Example 68(4) in tetrahydrofuran was added at room temperature thionyl chloride (0.37 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (15 mL) was carefully poured. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (15 mL), sodium iodide (0.37 g), sodium carbonate (0.27 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.42 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[1-(4-methoxyphenyl)-

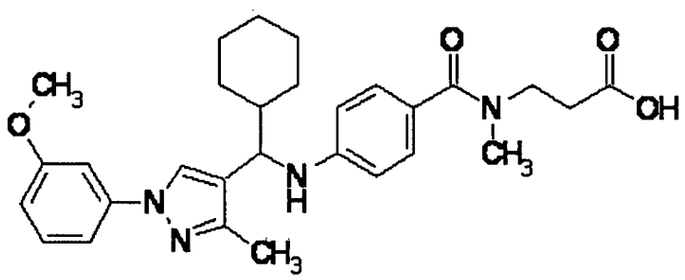
3-(morpholin-4-ylmethyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.38 g) as a pale-yellow oil. This was dissolved in ethanol (2 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.12 g, 12%) as a colorless solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.89 - 2.10 (m, 11 H), 2.50 - 2.75 (m, 6 H), 3.07 (s, 3 H), 3.50 - 3.85 (m, 6 H), 3.88 (s, 3 H), 4.17 - 4.25 (m, 2 H), 4.70 - 4.78 (m, 1 H), 6.83 (d, J=8.7 Hz, 2 H), 7.02 (d, J=9.0 Hz, 2 H), 7.19 - 7.35 (m, 4 H), 7.77 (s, 1 H).

[0646]

Example 70

3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0647]



[0648]

(1) methyl 1-(3-methoxyphenyl)-3-methyl-1H-pyrazole-4-carboxylate

Methyl 3-methyl-1H-pyrazole-4-carboxylate (4.6 g) synthesized in Example 1(3) was dissolved in N,N-dimethylacetamide (50 mL), 3-methoxyphenylboronic acid (10.0 g), copper acetate (12.0 g) and pyridine (10.6 mL) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite , 1N hydrochloric

acid (100 mL) was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (3.9 g, 48%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.56 (s, 3 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 6.80 - 8.33 (m, 5 H).

[0649]

(2) 1-(3-methoxyphenyl)-3-methyl-1H-pyrazole-4-carbaldehyde

A solution (20 mL) of methyl 1-(3-methoxyphenyl)-3-methyl-1H-pyrazole-4-carboxylate (3.9 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (80 mL) of lithium aluminum hydride (0.6 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr. The mixture was ice-cooled again, and water (1.6 mL), 1N aqueous sodium hydroxide solution (7.8 mL) and water (1.6 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (1.9 g) of 1-(3-methoxyphenyl)-3-methyl-1H-pyrazole-4-methanol as a pale-yellow oil. This was dissolved in toluene (30 mL), manganese dioxide (3.0 g) was added, and the mixture was heated for 30 min with a Dean-Stark trap. The reaction mixture was allowed to cool to room temperature, and manganese dioxide was collected by filtration. The solvent was evaporated under reduced pressure to give the title object compound (1.2 g, 64%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.59 (s, 3 H), 3.88 (s, 3 H), 6.80 - 7.40 (m, 4 H), 8.32 (s, 1 H), 10.00 (s, 1 H).

[0650]

(3) cyclohexyl[1-(3-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methanol

To a solution (15 mL) of in 1-(3-methoxyphenyl)-3-methyl-1H-pyrazole-4-carbaldehyde (0.62 g) synthesized in the above-mentioned (2) in tetrahydrofuran under ice-cooling was added dropwise cyclohexylmagnesium bromide (4.3 mL, 1M tetrahydrofuran solution). After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.60 g, 70%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 2.10 (m, 12 H), 2.34 (s, 3 H), 3.87 (s, 3 H), 4.43 (d, J=7.2 Hz, 1 H), 6.70 - 7.40 (m, 4 H), 7.78 (s, 1 H).

[0651]

(4) 3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (3 mL) of cyclohexyl[1-(3-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methanol (0.30 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added at room temperature thionyl chloride (0.11 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (5 mL) was carefully poured. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (5 mL), sodium iodide (0.23 g), sodium carbonate (0.16 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.25 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was

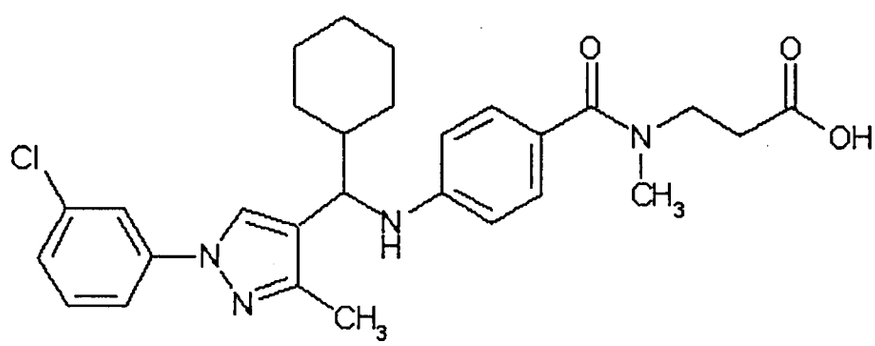
added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.38 g) as a pale-yellow oil. This was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (1.5 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.5 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.17 g, 34%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 2.03 (m, 11 H), 2.35 (s, 3 H), 2.70 (t, J=6.2 Hz, 2 H), 3.06 (s, 3 H), 3.71 (t, J=6.2 Hz, 2 H), 3.85 (s, 3 H), 4.19 (d, J=6.1 Hz, 1 H), 6.50 (d, J=8.0 Hz, 2 H), 6.76 (dd, J=7.8, 2.1 Hz, 1 H), 7.09 - 7.37 (m, 5 H), 7.67 (br. s., 1 H).

[0652]

Example 71

3-[{[4-({[1-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoic acid

[0653]




[0654]

(1) methyl 1-(3-chlorophenyl)-3-methyl-1H-pyrazole-4-

carboxylate

Methyl 3-methyl-1H-pyrazole-4-carboxylate (1.6 g) synthesized in Example 1(3) was dissolved in N,N-dimethylacetamide (30 mL), 3-chlorophenylboronic acid (3.58 g), copper acetate (5.0 g) and pyridine (4.0 mL) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, 1N hydrochloric acid (50 mL) was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (1.9 g, 67%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.55 (s, 3 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 6.70 - 8.35 (m, 5 H).

[0655]

(2) 1-(3-chlorophenyl)-3-methyl-1H-pyrazole-4-carbaldehyde

A solution (20 mL) of methyl 1-(3-chlorophenyl)-3-methyl-1H-pyrazole-4-carboxylate (1.9 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (80 mL) of lithium aluminum hydride (0.29 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr. The mixture was ice-cooled again, and water (0.80 mL), 1N aqueous sodium hydroxide solution (4.0 mL) and water (0.80 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (0.65 g) of 1-(3-chlorophenyl)-3-methyl-1H-pyrazole-4-methanol as a pale-yellow oil. This was dissolved in toluene (30 mL), manganese dioxide (2.0 g) was added, and the mixture was heated for 30 min with a Dean-Stark trap. The reaction mixture was allowed to cool to room temperature, and manganese dioxide was collected by filtration. The solvent was evaporated under

reduced pressure to give the title object compound (0.35 g, 23%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.59 (s, 3 H), 3.88 (s, 3 H), 7.20 - 7.80 (m, 4 H), 8.34 (s, 1 H), 10.00 (s, 1 H).

[0656]

(3) cyclohexyl[1-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]methanol

To a solution (5 mL) of 1-(3-chlorophenyl)-3-methyl-1H-pyrazole-4-carbaldehyde (0.35 g) synthesized in the above-mentioned (2) in tetrahydrofuran under ice-cooling was added dropwise cyclohexylmagnesium bromide (2.4 mL, 1M tetrahydrofuran solution). After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.25 g, 51%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 - 1.97 (m, 12 H), 2.33 (s, 3 H), 4.44 (d, J=7.2 Hz, 1 H), 7.20 -7.78 (m, 5 H).

[0657]

(4) 3-[{[4-({cyclohexyl[1-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (3 mL) of cyclohexyl[1-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]methanol (0.25 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added at room temperature thionyl chloride (0.10 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (5 mL) was carefully poured. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium

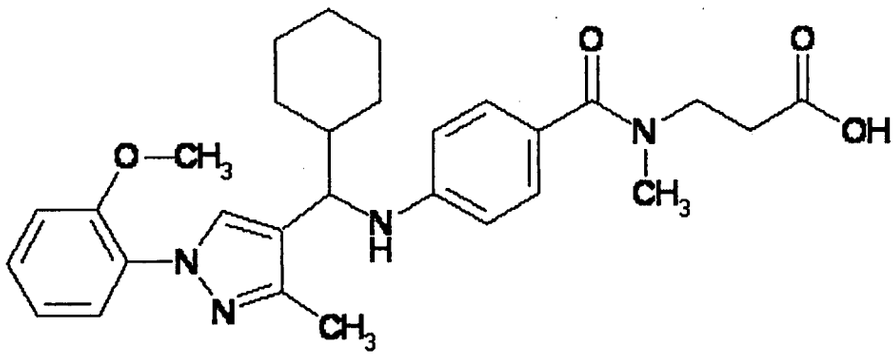
sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (5 mL), sodium iodide (0.19 g), sodium carbonate (0.13 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.20 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[1-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.35 g) as a pale-yellow oil. This was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (1.5 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.5 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.24 g, 58%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 - 2.07 (m, 11 H), 2.36 (s, 3 H), 2.71 (t, J=6.4 Hz, 2 H), 3.07 (s, 3 H), 3.72 (t, J=6.4 Hz, 2 H), 4.19 (d, J=6.1 Hz, 1 H), 6.48 (d, J=8.7 Hz, 2 H), 7.12 - 7.73 (m, 7 H).

[0658]

Example 72

3-[{[4-({[1-(2-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoic acid

[0659]



[0660]

(1) methyl 1-(2-methoxyphenyl)-3-methyl-1H-pyrazole-4-carboxylate

Methyl 3-methyl-1H-pyrazole-4-carboxylate (7.3 g) synthesized in Example 1(3) was dissolved in N,N-dimethylacetamide (150 mL), 2-methoxyphenylboronic acid (15.9 g), copper acetate (18.2 g) and pyridine (16.2 mL) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, 1N hydrochloric acid (100 mL) was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (10.3 g, 80%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.55 (s, 3 H), 3.85 (s, 3 H), 6.80 - 8.50 (m, 5 H).

[0661]

(2) 1-(2-methoxyphenyl)-3-methyl-1H-pyrazole-4-carbaldehyde

A solution (50 mL) of methyl 1-(2-methoxyphenyl)-3-methyl-1H-pyrazole-4-carboxylate (10.3 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (350 mL) of lithium aluminum hydride (1.6 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr. The mixture was ice-cooled again, and water (4.2 mL), 1N aqueous sodium

hydroxide solution (21.0 mL) and water (4.2 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (2.5 g) of 1-(2-methoxyphenyl)-3-methyl-1H-pyrazole-4-methanol as a pale-yellow oil. This was dissolved in toluene (50 mL), manganese dioxide (1.0 g) was added, and the mixture was heated under reflux with a Dean-Stark trap for 1 hr. The reaction mixture was allowed to cool to room temperature, and manganese dioxide was collected by filtration. The solvent was evaporated under reduced pressure to give the title object compound (2.2 g, 87%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.58 (s, 3 H), 3.92 (s, 3 H), 7.00 - 7.80 (m, 4 H), 8.50 (s, 1 H), 9.99 (s, 1 H).

[0662]

(3) cyclohexyl[1-(2-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methanol

To a solution (15 mL) of 1-(2-methoxyphenyl)-3-methyl-1H-pyrazole-4-carbaldehyde (1.5 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added dropwise under ice-cooling cyclohexylmagnesium bromide (11.0 mL, 1M tetrahydrofuran solution). After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (1.1 g, 53%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 2.10 (m, 12 H), 2.34 (s, 3 H), 3.87 (s, 3 H), 4.43 (dd, J=7.6, 3.0 Hz, 1 H), 7.00 - 7.75 (m, 4 H), 7.92 (s, 1 H).

[0663]

(4) 3-[{[4-({cyclohexyl[1-(2-methoxyphenyl)-3-methyl-1H-

pyrazol-4-
yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (5 mL) of cyclohexyl[1-(2-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methanol (0.40 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added at room temperature thionyl chloride (0.15 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (5 mL) was carefully poured. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (5.0 mL), sodium iodide (0.30 g), sodium carbonate (0.21 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.33 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[1-(2-methoxyphenyl)-3-methyl-1H-pyrazol-4-
yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.10 g) as a pale-yellow oil. This was dissolved in ethanol (1.0 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.04 g, 6%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.83 - 1.97 (m, 11 H), 2.26 (s, 3 H), 2.69 (br. s., 2 H), 3.03 (s, 3 H), 3.62 - 3.78 (m, 2 H), 3.82 (s, 3 H), 4.20 (d, J=6.6 Hz, 1 H), 6.93 - 7.70 (m, 9 H).

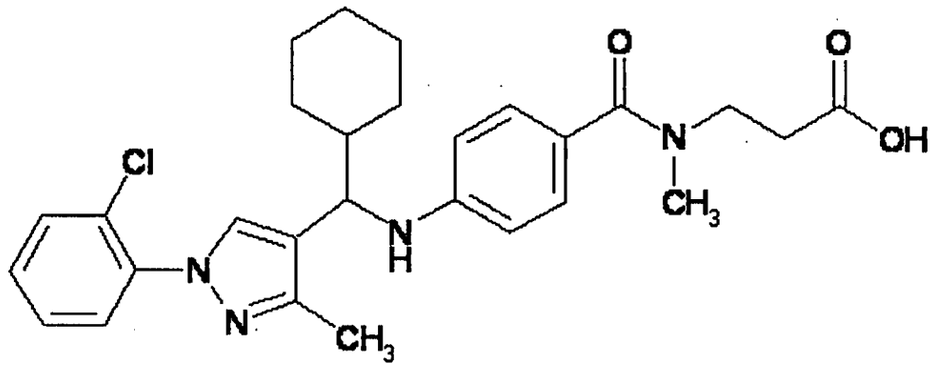
[0664]

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Example 73

3-[{[4-({[1-(2-chlorophenyl)-3-methyl-1H-pyrazol-4-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoic acid

[0665]




[0666]

(1) methyl 1-(2-chlorophenyl)-3-methyl-1H-pyrazole-4-carboxylate

Methyl 3-methyl-1H-pyrazole-4-carboxylate (4.5 g) synthesized in Example 1(3) was dissolved in N,N-dimethylacetamide (100 mL), 2-chlorophenylboronic acid (10.0 g), copper acetate (11.7 g) and pyridine (10.4 mL) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, 1N hydrochloric acid (100 mL) was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (2.0 g, 25%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.55 (s, 3 H), 3.85 (s, 3 H), 6.79 - 7.40 (m, 5 H).

[0667]

(2) 1-(2-chlorophenyl)-3-methyl-1H-pyrazole-4-carbaldehyde

A solution (20 mL) of methyl 1-(2-chlorophenyl)-3-methyl-1H-pyrazole-4-carboxylate (2.0 g) synthesized in the above-

mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (20 mL) of lithium aluminum hydride (0.30 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr. The mixture was ice-cooled again, and water (0.80 mL), 1N aqueous sodium hydroxide solution (4.0 mL) and water (0.80 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (0.36 g) of 1-(2-chlorophenyl)-3-methyl-1H-pyrazole-4-methanol as a pale-yellow oil. This was dissolved in toluene (10 mL), manganese dioxide (2.0 g) was added, and the mixture was heated under reflux with a Dean-Stark trap for 1 hr. The reaction mixture was allowed to cool to room temperature, and manganese dioxide was collected by filtration. The solvent was evaporated under reduced pressure to give the title object compound (0.27 g, 15%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.59 (s, 3 H), 7.00 - 7.70 (m, 4 H), 8.32 (s, 1 H), 10.02 (s, 1 H).

[0668]

(3) cyclohexyl[1-(2-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]methanol

To a solution (5 mL) of 1-(2-chlorophenyl)-3-methyl-1H-pyrazole-4-carbaldehyde (0.27 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added dropwise under ice-cooling cyclohexylmagnesium bromide (2.0 mL, 1M tetrahydrofuran solution). After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.29 g, 79%) as a pale-yellow oil.

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$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 2.20 (m, 12 H), 2.35 (s, 3 H), 4.45 (d, J=7.2 Hz, 1 H), 7.20 - 7.60 (m, 4 H), 7.76 (s, 1 H).

[0669]

(4) 3-[{[4-({cyclohexyl[1-(2-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (5 mL) of cyclohexyl[1-(2-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]methanol (0.29 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added at room temperature thionyl chloride (0.11 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (3 mL) was carefully poured. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (5.0 mL), sodium iodide (0.21 g), sodium carbonate (0.15 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.24 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[1-(2-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.24 g) as a pale-yellow oil. This was dissolved in ethanol (2.0 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the

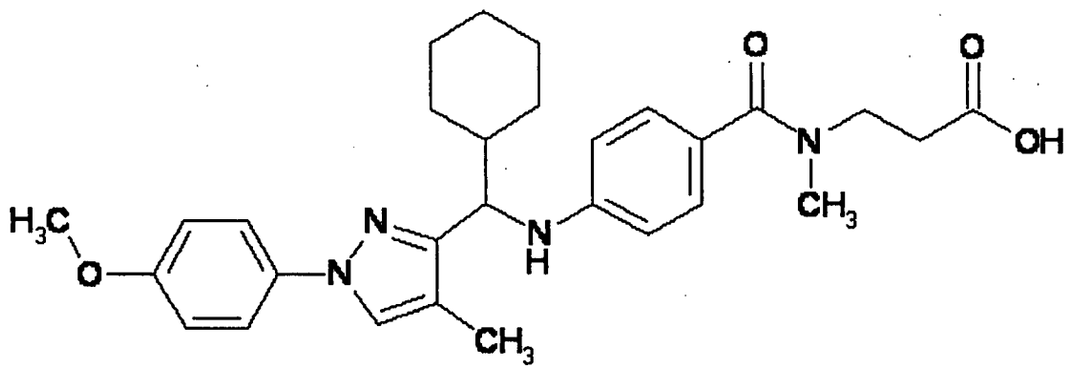
title object compound (0.18 g, 37%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 2.08 (m, 11 H), 2.34 (s, 3 H), 2.65 - 2.80 (m, 2 H), 3.08 (s, 3 H), 3.73 (br. s., 2 H), 4.23 (d, J=6.1 Hz, 1 H), 6.54 (br. s., 2 H), 7.29 - 7.79 (m, 7 H).

[0670]

Example 74

3-[{[4-({cyclohexyl[1-(4-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0671]



[0672]

(1) ethyl 1-(4-methoxyphenyl)-4-methyl-1H-pyrazole-3-carboxylate

Ethyl 4-methyl-1H-pyrazole-3-carboxylate (2.58 g) was dissolved in N,N-dimethylacetamide (50 mL), 4-methoxyphenylboronic acid (5.0 g), copper acetate (6.0 g) and pyridine (5.3 mL) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, 1N hydrochloric acid (50 mL) was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (2.7 g, 66%) as a pale-yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.21 (t, J=7.2 Hz, 3 H), 2.33 (s, 3 H), 3.85 (s, 3 H), 4.22 (q, J=7.2 Hz, 2 H), 6.94 (d, J=9.0

Hz, 2 H), 7.28 (d, J=9.0 Hz, 2 H), 7.50 (s, 1 H).

[0673]

(2) 1-(4-methoxyphenyl)-4-methyl-1H-pyrazole-3-carbaldehyde

A solution (10 mL) of ethyl 1-(4-methoxyphenyl)-4-methyl-1H-pyrazole-3-carboxylate (2.7 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (20 mL) of lithium aluminum hydride (0.40 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr. The mixture was ice-cooled again, and water (1.0 mL), 1N aqueous sodium hydroxide solution (5.0 mL) and water (1.0 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (1.38 g) of 1-(4-methoxyphenyl)-4-methyl-1H-pyrazole-3-methanol as a pale-yellow oil. This was dissolved in toluene (30 mL), manganese dioxide (2.0 g) was added, and the mixture was heated under reflux with a Dean-Stark trap for 1 hr. The reaction mixture was allowed to cool to room temperature, and manganese dioxide was collected by filtration. The solvent was evaporated under reduced pressure to give the title object compound (0.96 g, 43%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.41 (s, 3 H), 3.87 (s, 3 H), 7.01 (d, J=8.7 Hz, 2 H), 7.38 (d, J=8.7 Hz, 2 H), 7.55 (s, 1 H), 9.88 (s, 1 H).

[0674]

(3) cyclohexyl[1-(4-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methanol

To a solution (10 mL) of 1-(4-methoxyphenyl)-4-methyl-1H-pyrazole-3-carbaldehyde (0.96 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added dropwise under ice-cooling cyclohexylmagnesium bromide (6.0 mL, 1M tetrahydrofuran solution). After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction

mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.70 g, 53%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.61 - 1.87 (m, 12 H), 2.19 (s, 3 H), 3.86 (s, 3 H), 4.34 (dd, J=9.7, 4.4 Hz, 1 H), 6.95 (d, J=9.0 Hz, 2 H), 7.32 (d, J=9.0 Hz, 2 H), 7.41 (s, 1 H).

[0675]

(4)3-[{[4-({cyclohexyl[1-(4-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (5 mL) of cyclohexyl[1-(4-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methanol (0.40 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added at room temperature thionyl chloride (0.15 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (3 mL) was carefully poured. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (10.0 mL), sodium iodide (0.30 g), sodium carbonate (0.21 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.34 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[1-(4-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.06

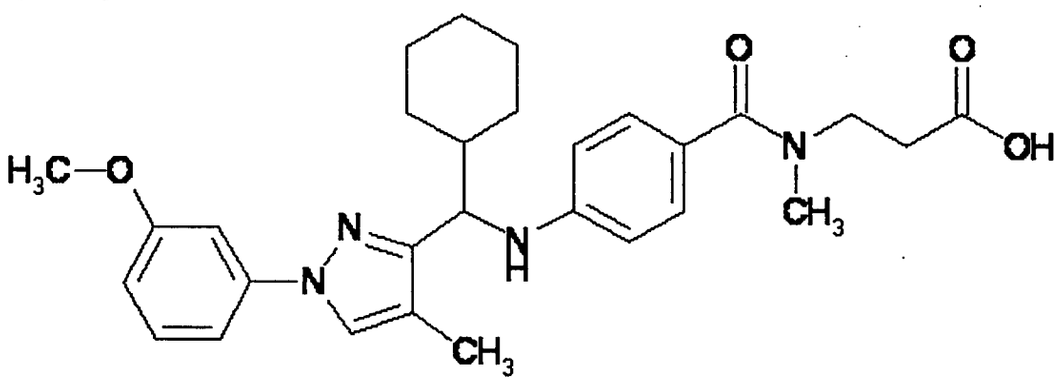
g) as a pale-yellow oil. This was dissolved in ethanol (1.0 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.04 g, 6%) as a pale-yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 - 2.07 (m, 11 H), 2.18 (s, 3 H), 2.71 (br. s., 2 H), 3.08 (s, 3 H), 3.72 (t, J=6.4 Hz, 2 H), 3.88 (s, 3 H), 4.24 (d, J=9.1 Hz, 1 H), 6.30 (d, J=8.7 Hz, 2 H), 6.94 (d, J=8.7 Hz, 2 H), 7.10 - 7.26 (m, 4 H), 7.37 (s, 1 H).

[0676]

Example 75

3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0677]




[0678]

(1) ethyl 1-(3-methoxyphenyl)-4-methyl-1H-pyrazole-3-carboxylate

Ethyl 4-methyl-1H-pyrazole-3-carboxylate (2.58 g) was dissolved in N,N-dimethylacetamide (50 mL), 3-methoxyphenylboronic acid (5.0 g), copper acetate (6.0 g) and pyridine (5.3 mL) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, 1N hydrochloric acid (50 mL) was added to the filtrate, and the mixture was extracted with diethyl ether.

The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (1.9 g, 46%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.43 (t, J=7.2 Hz, 3 H), 2.37 (s, 3 H), 3.87 (s, 3 H), 4.43 (q, J=7.2 Hz, 2 H), 6.94 -7.50 (m, 5 H).

[0679]

(2) 1-(3-methoxyphenyl)-4-methyl-1H-pyrazole-3-carbaldehyde

A solution (5 mL) of ethyl 1-(3-methoxyphenyl)-4-methyl-1H-pyrazole-3-carboxylate (1.9 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (20 mL) of lithium aluminum hydride (0.29 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr. The mixture was ice-cooled again, and water (0.76 mL), 1N aqueous sodium hydroxide solution (3.8 mL) and water (0.76 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (0.99 g) of 1-(3-methoxyphenyl)-4-methyl-1H-pyrazole-3-methanol as a pale-yellow oil. This was dissolved in toluene (15 mL), manganese dioxide (0.32 g) was added, and the mixture was heated under reflux with a Dean-Stark trap for 1 hr. The reaction mixture was allowed to cool to room temperature, and manganese dioxide was collected by filtration. The filtrate was concentrated under reduced pressure to give the title object compound (0.84 g, 54%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.39 (s, 3 H), 3.89 (s, 3 H), 6.80 - 7.45 (m, 4 H), 7.74 (s, 1 H), 10.13 (s, 1 H).

[0680]

(3) cyclohexyl[1-(3-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methanol

To a solution (10 mL) of 1-(3-methoxyphenyl)-4-methyl-1H-

pyrazole-3-carbaldehyde (0.84 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added dropwise under ice-cooling cyclohexylmagnesium bromide (7.0 mL, 1M tetrahydrofuran solution). After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.62 g, 52%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.99 - 2.00 (m, 12 H), 2.12 (s, 3 H), 3.86 (s, 3 H), 4.52 (t, J=6.6 Hz, 1 H), 6.75 - 7.32 (m, 4 H), 7.64 (s, 1 H).

[0681]

(4) 3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (5 mL) of cyclohexyl[1-(3-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methanol (0.52 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added at room temperature thionyl chloride (0.19 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (3 mL) was carefully poured. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (10.0 mL), sodium iodide (0.39 g), sodium carbonate (0.28 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.38 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted

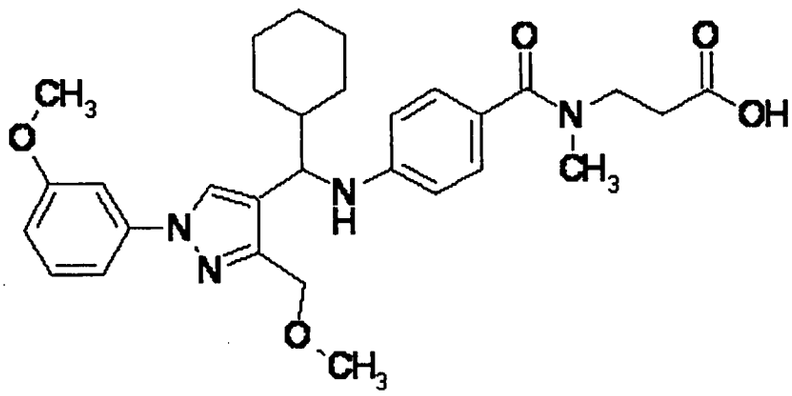
with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.16 g) as a pale-yellow oil. This was dissolved in ethanol (2.0 mL), 1N aqueous sodium hydroxide solution (1.5 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.5 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.09 g, 11%) as a pale-yellow solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 - 2.06 (m, 11 H), 2.09 (s, 3 H), 2.73 (t, J=6.2 Hz, 2 H), 3.08 (s, 3 H), 3.72 (t, J=6.2 Hz, 2 H), 3.87 (s, 3 H), 4.40 (d, J=7.2 Hz, 1 H), 6.62 (d, J=8.7 Hz, 2 H), 6.78 (dd, J=7.8, 2.1 Hz, 1 H), 7.10 - 7.50 (m, 5 H), 7.57 (s, 1 H).

[0682]

Example 76

3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0683]



[0684]

(1) methyl 3-(methoxymethyl)-1-(3-methoxyphenyl)-1H-pyrazole-4-carboxylate

To a solution of methyl 3-(methoxymethyl)-1-phenyl-1H-pyrazole-4-carboxylate (2.8 g) synthesized in Example 37(1) in N,N-dimethylacetamide (50 mL) were added 3-methoxyphenylboronic acid (5.0 g), copper acetate (6.0 g) and pyridine (5.3 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, 1N hydrochloric acid (50 mL) was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (1.1 g, 23%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.51 (s, 3 H), 3.87 (s, 3 H), 3.92 (s, 3 H), 4.80 (s, 2 H), 7.29 - 7.93 (m, 4 H), 8.37 (s, 1 H).

[0685]

(2) 3-(methoxymethyl)-1-(3-methoxyphenyl)-1H-pyrazole-4-carbaldehyde

A solution (5 mL) of methyl 3-(methoxymethyl)-1-(3-methoxyphenyl)-1H-pyrazole-4-carboxylate (1.1 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (10 mL) of lithium aluminum hydride (0.25 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr. The mixture was ice-cooled again, and water (0.38 mL), 1N aqueous sodium hydroxide solution (1.9 mL) and water (0.38 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (0.68 g) of 3-(methoxymethyl)-1-(3-methoxyphenyl)-1H-pyrazole-4-methanol as a pale-yellow oil. This was dissolved in toluene (15 mL), manganese dioxide (1.0 g) was added, and the mixture was heated under reflux with a Dean-Stark trap for 1 hr. The reaction mixture was allowed to cool to room temperature, and

manganese dioxide was collected by filtration. The solvent was evaporated under reduced pressure to give the title object compound (0.30 g, 32%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.50 (s, 3 H), 3.88 (s, 3 H), 4.80 (s, 2 H), 6.91 (dd, J=8.3, 1.5 Hz, 1 H), 7.16 - 7.49 (m, 3 H), 8.40 (s, 1 H), 10.07 (s, 1 H).

[0686]

(3) cyclohexyl[3-(methoxymethyl)-1-(3-methoxyphenyl)-1H-pyrazol-4-yl]methanol

To a solution (5 mL) of 3-(methoxymethyl)-1-(3-methoxyphenyl)-1H-pyrazole-4-carbaldehyde (0.30 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added dropwise under ice-cooling cyclohexylmagnesium bromide (2.0 mL, 1M tetrahydrofuran solution). After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.40 g, quantitative) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.89 - 2.21 (m, 11 H), 3.04 (br.s, 1 H), 3.44 (s, 3 H), 3.87 (s, 3 H), 4.41 (d, J=7.7 Hz, 1 H), 4.61 (d, J=3.6 Hz, 2 H), 6.82 (ddd, J=8.1, 2.5, 0.8 Hz, 1 H), 7.14 - 7.40 (m, 3 H), 7.77 (s, 1 H).

[0687]

(4) 3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (5 mL) of cyclohexyl[3-(methoxymethyl)-1-(3-methoxyphenyl)-1H-pyrazol-4-yl]methanol (0.40 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added at room temperature thionyl chloride (0.14 mL). The reaction mixture was stirred at room temperature for 30 min

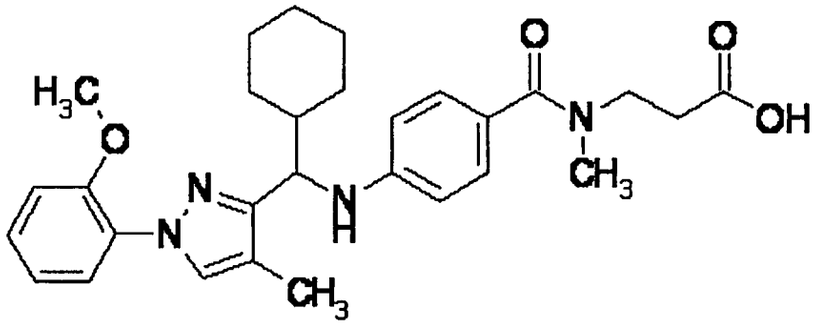
and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (3 mL) was carefully poured. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (5.0 mL), sodium iodide (0.23 g), sodium carbonate (0.18 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.25 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.11 g) as a pale-yellow oil. This was dissolved in ethanol (3.0 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.07 g, 10%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 2.12 (m, 11 H), 2.73 (t, J=6.5 Hz, 2 H), 3.07 (s, 3 H), 3.41 (s, 3 H), 3.72 (t, J=6.5 Hz, 2 H), 3.85 (s, 3 H), 4.34 (d, J=7.2 Hz, 1 H), 4.57 (s, 2 H), 6.57 (d, J=8.7 Hz, 2 H), 6.79 (dt, J=8.2, 1.3 Hz, 1 H), 7.11 - 7.38 (m, 5 H), 7.72 (s, 1 H).

[0688]

Example 77

3-[{[4-({cyclohexyl[1-(2-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0689]



[0690]

(1) ethyl 1-(2-methoxyphenyl)-4-methyl-1H-pyrazole-3-carboxylate

Ethyl 4-methyl-1H-pyrazole-3-carboxylate (4.0 g) was dissolved in N,N-dimethylacetamide (30 mL), 2-methoxyphenylboronic acid (7.9 g), copper acetate (9.5 g) and pyridine (8.4 mL) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, 1N hydrochloric acid (50 mL) was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (1.6 g, 25%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.41 (t, J=7.2 Hz, 3 H), 2.37 (s, 3 H), 3.87 (s, 3 H), 4.43 (q, J=7.2 Hz, 2 H), 7.00 - 7.45 (m, 4 H), 7.78 (s, 1 H).

[0691]

(2) 1-(2-methoxyphenyl)-4-methyl-1H-pyrazole-3-carbaldehyde

A solution (5 mL) of ethyl 1-(2-methoxyphenyl)-4-methyl-1H-pyrazole-3-carboxylate (1.6 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (10 mL) of lithium aluminum hydride (0.50 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr, ice-cooled again, and water (1.3 mL), 1N aqueous sodium hydroxide

solution (6.5 mL) and water (1.3 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (0.79 g) of 1-(2-methoxyphenyl)-4-methyl-1H-pyrazole-3-methanol as a pale-yellow oil. This was dissolved in toluene (20 mL), manganese dioxide (2.0 g) was added, and the mixture was heated under reflux with a Dean-Stark trap for 1 hr. The reaction mixture was allowed to cool to room temperature, and manganese dioxide was collected by filtration. The solvent was evaporated under reduced pressure to give the title object compound (0.97 g, 70%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.39 (s, 3 H), 3.90 (s, 3 H), 7.00 - 7.45 (m, 3 H), 7.64 - 7.84 (m, 2 H), 10.13 (s, 1 H).

[0692]

(3)cyclohexyl[1-(2-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methanol

To a solution (10 mL) of 1-(2-methoxyphenyl)-4-methyl-1H-pyrazole-3-carbaldehyde (0.97 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added dropwise under ice-cooling cyclohexylmagnesium bromide (5.0 mL, 1M tetrahydrofuran solution). After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.56 g, 40%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.99 - 2.00 (m, 12 H), 2.12 (s, 3 H), 3.86 (s, 3 H), 4.52 (t, J=6.6 Hz, 1 H), 6.75 - 7.32 (m, 4 H), 7.64 (s, 1 H).

[0693]

(4)3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-4-methyl-1H-

pyrazol-3-
yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (5 mL) of cyclohexyl[1-(2-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methanol (0.45 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added thionyl chloride (0.17 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min, ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (3 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (10.0 mL), sodium iodide (0.33 g), sodium carbonate (0.24 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.38 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[1-(2-methoxyphenyl)-4-methyl-1H-pyrazol-3-
yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.09 g) as a pale-yellow oil. This was dissolved in ethanol (2.0 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.06 g, 8%) as a pale-yellow solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 - 2.07 (m, 11 H), 2.10 (s, 3 H), 2.73 (t, J=6.2 Hz, 2 H), 3.09 (s, 3 H), 3.72 (t, J=6.2 Hz, 2 H), 3.86 (s, 3 H), 4.41 (d, J=7.2 Hz, 1 H), 6.62 (d, J=8.3 Hz, 2 H), 6.96 - 7.37 (m, 5 H), 7.63 (d, J=8.0 Hz, 1 H), 7.70

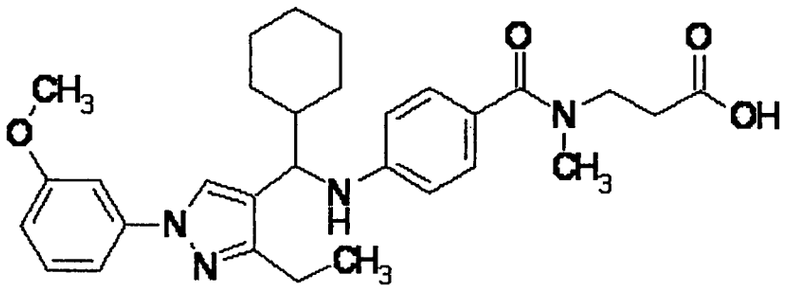
(s, 1 H).

[0694]

Example 78

3-[{[4-({cyclohexyl[3-ethyl-1-(3-methoxyphenyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0695]



[0696]

(1)methyl 3-ethyl-1-(3-methoxyphenyl)-1H-pyrazole-4-carboxylate

Methyl 3-ethyl-1H-pyrazole-4-carboxylate (2.5 g) synthesized in Example 39(1) was dissolved in N,N-dimethylacetamide (50 mL), 3-methoxyphenylboronic acid (5.0 g), copper acetate (6.0 g) and pyridine (5.3 mL) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, 1N hydrochloric acid (50 mL) was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (2.3 g, 54%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.32 (t, J=7.5 Hz, 3 H), 2.98 (q, J=7.5 Hz, 2 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 6.86 (ddd, J=8.2, 2.5, 0.9 Hz, 1 H), 7.16 - 7.46 (m, 3 H), 8.32 (s, 1 H).

[0697]

(2)3-ethyl-1-(3-methoxyphenyl)-1H-pyrazole-4-carbaldehyde

A solution (5 mL) of methyl 3-ethyl-1-(3-methoxyphenyl)-

1H-pyrazole-4-carboxylate (2.3 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (15 mL) of lithium aluminum hydride (0.34 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr, ice-cooled again, and water (0.88 mL), 1N aqueous sodium hydroxide solution (4.4 mL), water (0.88 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (2.3 g) of 3-ethyl-1-(3-methoxyphenyl)-1H-pyrazole-4-methanol as a pale-yellow oil. This was dissolved in toluene (50 mL), manganese dioxide (4.0 g) was added, and the mixture was heated under reflux with a Dean-Stark trap for 1 hr. The reaction mixture was allowed to cool to room temperature, manganese dioxide was collected by filtration, and the solvent was evaporated under reduced pressure to give the title object compound (1.9 g, 94%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.35 (t, J=7.6 Hz, 3 H), 2.99 (q, J=7.6 Hz, 2 H), 3.88 (s, 3 H), 6.89 (dd, J=8.3, 1.5 Hz, 1 H), 7.11 - 7.50 (m, 3 H), 8.33 (s, 1 H), 10.00 (s, 1 H).

[0698]

(3)cyclohexyl[3-ethyl-1-(3-methoxyphenyl)-1H-pyrazol-4-yl]methanol

To a solution (20 mL) of 3-ethyl-1-(3-methoxyphenyl)-1H-pyrazole-4-carbaldehyde (1.9 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added dropwise under ice-cooling cyclohexylmagnesium bromide (12.0 mL, 1M tetrahydrofuran solution). After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure to give a crude product (2.6 g, quantitative) of the title object compound as a pale-

yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 - 1.98 (m, 14 H), 2.71 (q, J=7.5 Hz, 2 H), 3.60 (br,s., 1 H), 3.87 (s, 3 H), 4.44 (d, J=7.3 Hz, 1 H), 6.78 (ddd, J=8.1, 2.4, 0.9 Hz, 1 H), 7.14 - 7.38 (m, 3 H), 7.78 (s, 1 H).

[0699]

(4)3-[{[4-({cyclohexyl[3-ethyl-1-(3-methoxyphenyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (5 mL) of cyclohexyl[3-ethyl-1-(3-methoxyphenyl)-1H-pyrazol-4-yl]methanol (0.31 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added thionyl chloride (0.13 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min, ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (3 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved indimethylacetamide (10.0 mL), sodium iodide (0.23 g), sodium carbonate (0.15 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.25 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[3-ethyl-1-(3-methoxyphenyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.16 g) as a pale-yellow oil. This was dissolved in ethanol (3.0 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the

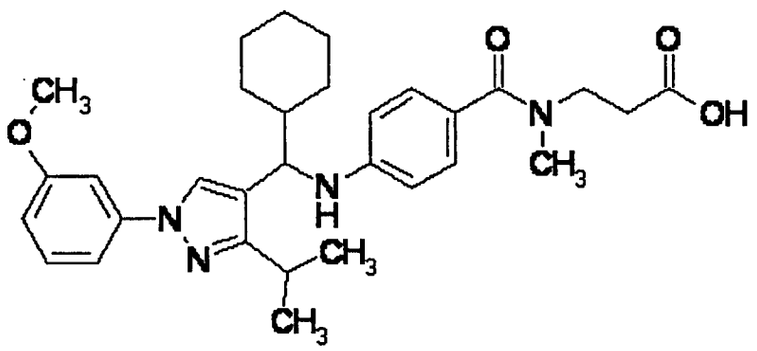
residue. The precipitate was washed with water to give the title object compound (0.12 g, 23%) as a pale-yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 - 2.07 (m, 14 H), 2.62 - 2.81 (m, 4 H), 3.07 (s, 3 H), 3.72 (t, J=6.0 Hz, 2 H), 3.85 (s, 3 H), 4.22 (d, J=5.8 Hz, 1 H), 6.51 (d, J=8.5 Hz, 2 H), 6.76 (dt, J=8.2, 1.2 Hz, 1 H), 7.10 - 7.37 (m, 5 H), 7.65 (s, 1 H).

[0700]

Example 79

3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0701]



[0702]

(1) methyl 1-(3-methoxyphenyl)-3-(propan-2-yl)-1H-pyrazole-4-carboxylate

Methyl 3-(1-methylethyl)-1H-pyrazole-4-carboxylate (2.8 g) synthesized in Example 7(1) was dissolved in N,N-dimethylacetamide (50 mL), 3-methoxyphenylboronic acid (5.0 g), copper acetate (6.0 g) and pyridine (5.3 mL) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, 1N hydrochloric acid (50 mL) was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (3.4 g, 75%) as a pale-

yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.36 (d, J=7.0 Hz, 6 H), 3.56 - 3.59 (m, 1 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 6.85 (ddd, J=8.1, 2.5, 1.0 Hz, 1 H), 7.18 - 7.45 (m, 3 H), 8.31 (s, 1 H).

[0703]

(2)1-(3-methoxyphenyl)-3-(propan-2-yl)-1H-pyrazole-4-carbaldehyde

A solution (15 mL) of methyl 1-(3-methoxyphenyl)-3-(propan-2-yl)-1H-pyrazole-4-carboxylate (3.4 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (35 mL) of lithium aluminum hydride (0.48 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr, ice-cooled again, and water (1.25 mL), 1N aqueous sodium hydroxide solution (6.3 mL), water (1.25 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (2.7 g) of 1-(3-methoxyphenyl)-3-(propan-2-yl)-1H-pyrazole-4-methanol as a pale-yellow oil. This was dissolved in toluene (50 mL), manganese dioxide (3.0 g) was added, and the mixture was heated under reflux with a Dean-Stark trap for 1 hr. The reaction mixture was allowed to cool to room temperature, and manganese dioxide was collected by filtration. The solvent was evaporated under reduced pressure to give the title object compound (2.6 g, 84%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.39 (d, J=6.8 Hz, 6 H), 3.48 - 3.52 (m, 1 H), 3.88 (s, 3 H), 6.88 (dd, J=7.8, 2.1 Hz, 1 H), 7.09 - 7.45 (m, 3 H), 8.33 (s, 1 H), 10.02 (s, 1 H).

[0704]

(3)cyclohexyl[1-(3-methoxyphenyl)-3-(propan-2-yl)-1H-pyrazol-4-yl]methanol

To a solution (20 mL) of 1-(3-methoxyphenyl)-3-(propan-2-yl)-1H-pyrazole-4-carbaldehyde (2.6 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added dropwise

cyclohexylmagnesium bromide (15.0 mL, 1M tetrahydrofuran solution) under ice-cooling. After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure to give a crude product (2.6 g, 75%) of the title object compound as a pale-yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 2.15 (m, 17 H), 3.00 - 3.20 (m, 1 H), 3.86 (s, 3 H), 4.46 (d, J=7.6 Hz, 1 H), 6.63 - 7.48 (m, 4 H), 7.77 (s, 1 H).

[0705]

(4)3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-3-(1-methylethyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (5 mL) of cyclohexyl[1-(3-methoxyphenyl)-3-(propan-2-yl)-1H-pyrazol-4-yl]methanol (0.45 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added thionyl chloride (0.18 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min, ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (5 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (10.0 mL), sodium iodide (0.30 g), sodium carbonate (0.21 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.34 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[1-(3-methoxyphenyl)-3-(1-

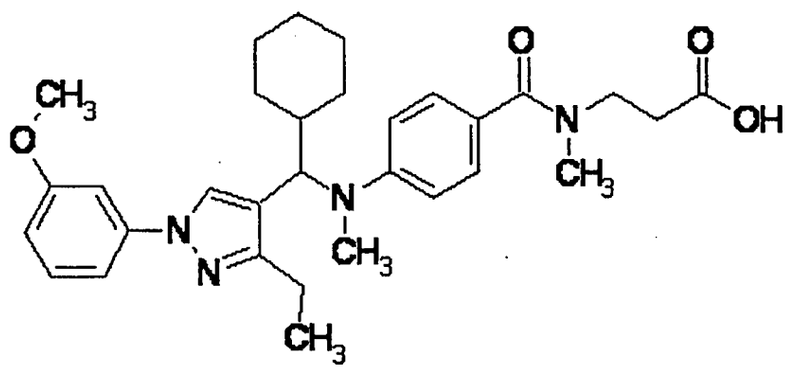
methylethyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.37 g) as a pale-yellow oil. This was dissolved in ethanol (5.0 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.28 g, 38%) as a pale-yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.27 (m, 11 H), 1.30 - 1.40 (m, 6 H), 2.73 (d, J=6.0 Hz, 2 H), 2.94 - 3.17 (m, 4 H), 3.73 (d, J=6.0 Hz, 2 H), 3.85 (s, 3 H), 4.26 (d, J=6.0 Hz, 1 H), 6.52 (d, J=8.7 Hz, 2 H), 6.75 (ddd, J=8.2, 2.5, 0.9 Hz, 1 H), 7.10 - 7.32 (m, 5 H), 7.62 (s, 1 H).

[0706]

Example 80

3-[({4-[{cyclohexyl[3-ethyl-1-(3-methoxyphenyl)-1H-pyrazol-4-yl]methyl}(methyl)amino]phenyl}carbonyl)(methyl)amino]-propanoic acid

[0707]



[0708]

To a solution of ethyl 3-[{[4-({cyclohexyl[3-ethyl-1-(3-methoxyphenyl)-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (1.1 g) synthesized in Example 78(4) in N,N-dimethylacetamide (5 mL) was added sodium hydride (0.16 g) under ice-cooling and, after stirring for 30 min, methyl iodide (0.37 mL) was added.

The ice bath was removed, the reaction mixture was stirred at room temperature overnight, saturated aqueous ammonium chloride solution was added and the mixture was extracted with diethyl ether. The extract was washed with brine to give ethyl 3-[({4-[{cyclohexyl[3-ethyl-1-(3-methoxyphenyl)-1H-pyrazol-4-yl]methyl}(methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate (0.23 g, 75%) as a pale-yellow oil. This was dissolved in ethanol (3.0 mL), 1N aqueous sodium hydroxide solution (1.5 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (1.5 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=10:1, volume ratio) to give the title object compound (0.10 g, 10%) as a pale-yellow solid.

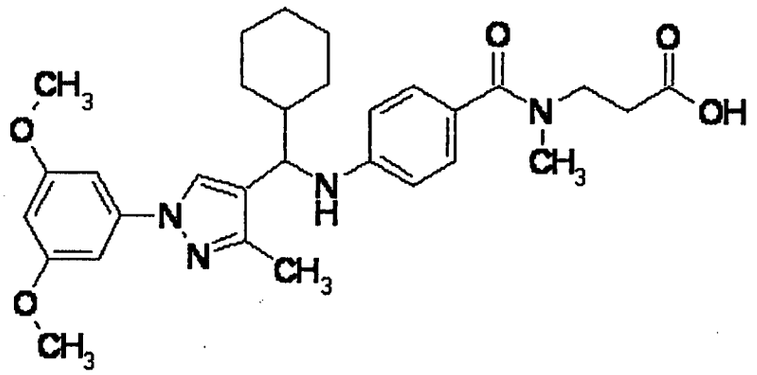
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.99 (m, 14 H), 2.17 (s, 3 H), 2.72 (q, J=7.4 Hz, 2 H), 2.76 - 2.90 (m, 2 H), 3.07 (s, 3 H), 3.75 - 3.85 (m, 5 H), 4.22 (d, J=5.3 Hz, 1 H), 6.50 (d, J=8.7 Hz, 2 H), 6.76 (d, J=8.3 Hz, 1 H), 7.07 - 7.43 (m, 5 H), 7.65 (s, 1 H).

[0709]

Example 81

3-[{[4-({cyclohexyl[1-(3,5-dimethoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0710]



[0711]

(1) methyl 1-(3,5-dimethoxyphenyl)-3-methyl-1H-pyrazole-4-carboxylate

Methyl 3-methyl-1H-pyrazole-4-carboxylate (3.9 g) synthesized in Example 1(3) was dissolved in N,N-dimethylacetamide (50 mL), 3,5-dimethoxyphenylboronic acid (10.0 g), copper acetate (10.0 g) and pyridine (8.9 mL) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, 1N hydrochloric acid (50 mL) was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (3.0 g, 40%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.55 (s, 3 H), 3.85 (s, 6 H), 6.41 (t, J=2.3 Hz, 1 H), 6.83 (d, J=2.3 Hz, 2 H), 8.30 (s, 1 H).

[0712]

(2)1-(3,5-dimethoxyphenyl)-3-methyl-1H-pyrazole-4-carbaldehyde

A solution (15 mL) of methyl 1-(3,5-dimethoxyphenyl)-3-methyl-1H-pyrazole-4-carboxylate (3.0 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (35 mL) of lithium aluminum hydride (0.42 g) in tetrahydrofuran. The ice bath was removed, and the reaction

mixture was stirred at room temperature for 1 hr, ice-cooled again, and water (1.1 mL), 1N aqueous sodium hydroxide solution (5.5 mL), water (1.1 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (2.7 g) of 1-(3,5-dimethoxyphenyl)-3-methyl-1H-pyrazole-4-methanol as a pale-yellow oil. This was dissolved in toluene (30 mL), manganese dioxide (2.0 g) was added, and the mixture was heated under reflux with a Dean-Stark trap for 1 hr. The reaction mixture was allowed to cool to room temperature, manganese dioxide was collected by filtration, and the solvent was evaporated under reduced pressure to give the title object compound (2.0 g, 74%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.55 (s, 3 H), 3.85 (s, 6 H), 6.44 (s, 1 H), 6.82 - 6.84 (m, 2 H), 8.30 (s, 1 H), 9.98 (s, 1 H).

[0713]

(3)cyclohexyl[1-(3,5-dimethoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methanol

To a solution (10 mL) of 1-(3,5-dimethoxyphenyl)-3-methyl-1H-pyrazole-4-carbaldehyde (2.0 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added dropwise cyclohexylmagnesium bromide (15.0 mL, 1M tetrahydrofuran solution) under ice-cooling. After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (2.6 g, 40%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.89 - 2.00 (m, 12 H), 2.33 (s, 3 H), 3.84 (s, 6 H), 4.40 - 4.45 (m, 1 H), 6.34 (t, J=2.1 Hz, 1

H), 6.81 (d, J=2.3 Hz, 2 H), 7.76 (s, 1 H).

[0714]

(4)3-[{[4-({cyclohexyl[1-(3,5-dimethoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (20 mL) of cyclohexyl[1-(3,5-dimethoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methanol (1.0 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added thionyl chloride (0.40 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min, ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (15 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (15.0 mL), sodium iodide (0.67 g), sodium carbonate (0.45 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.75 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[1-(3,5-dimethoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.74 g) as a pale-yellow oil. This was dissolved in ethanol (5.0 mL), 1N aqueous sodium hydroxide solution (3.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (3.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.46 g, 29%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 - 2.02 (m, 11 H), 2.35 (s, 3

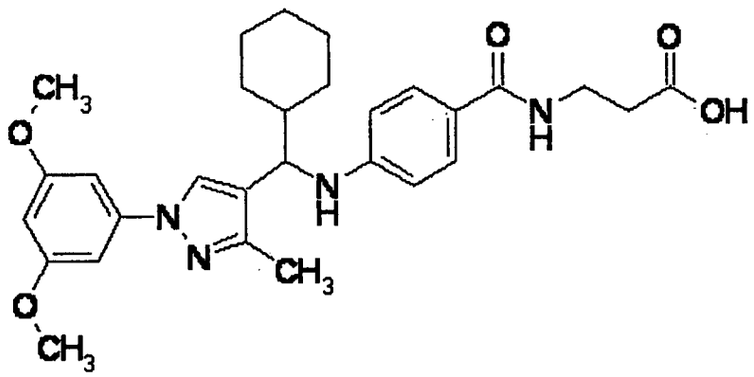
H), 2.70 (br. s., 2 H), 3.06 (s, 3 H), 3.71 (t, J=6.4 Hz, 2 H), 3.82 (s, 6 H), 4.18 (d, J=5.8 Hz, 1 H), 6.32 (t, J=2.2 Hz, 1 H), 6.49 (d, J=8.7 Hz, 2 H), 6.77 (s, 2 H), 7.26 (d, 2 H), 7.64 (s, 1 H).

[0715]

Example 82

3-({[4-({cyclohexyl[1-(3,5-dimethoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0716]



[0717]

To a solution (20 mL) of cyclohexyl[1-(3,5-dimethoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methanol (1.0 g) synthesized in Example 81(3) in tetrahydrofuran was added at room temperature thionyl chloride (0.40 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (15 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (15.0 mL), sodium iodide (0.67 g), sodium carbonate (0.45 g) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.70 g) synthesized in Example 1(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted

with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-({[4-({cyclohexyl[1-(3,5-dimethoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoate (1.3 g) as a pale-yellow oil. This was dissolved in ethanol (5.0 mL), 1N aqueous sodium hydroxide solution (3.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (3.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.65 g, 42%) as a colorless solid.

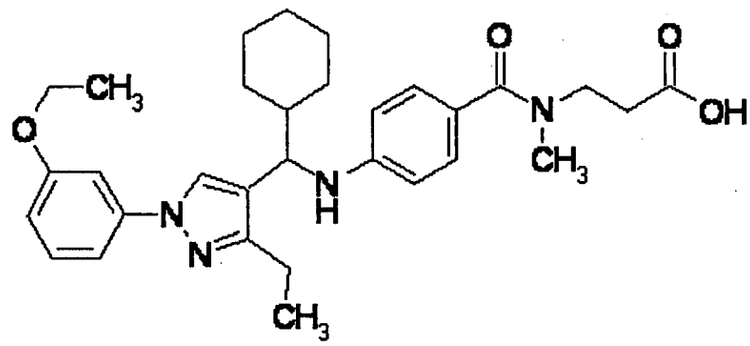
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 1.98 (m, 11 H), 2.35 (s, 3 H), 2.65 (t, J=6.0 Hz, 2 H), 3.66 (d, J=6.0 Hz, 2 H), 3.80 (s, 6 H), 4.20 (d, J=6.0 Hz, 1 H), 6.31 (t, J=2.2 Hz, 1 H), 6.49 (d, J=8.7 Hz, 2 H), 6.60 (d, J=6.0 Hz, 1 H), 6.75 (s, 2 H), 7.53 (d, J=8.9 Hz, 2 H), 7.62 (s, 1 H).

[0718]

Example 83

3-[{[4-({cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0719]



[0720]

(1) methyl 1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazole-4-carboxylate

Methyl 3-ethyl-1H-pyrazole-4-carboxylate (6.9 g)

synthesized in Example 39(1) was dissolved in N,N-dimethylacetamide (150 mL), 3-ethoxyphenylboronic acid (15.0 g), copper acetate (16.4 g) and pyridine (14.5 mL) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, 1N hydrochloric acid (70 mL) was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (4.4 g, 36%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.32 (t, J=7.5 Hz, 3 H), 1.44 (t, J=7.0 Hz, 3 H), 2.98 (q, J=7.5 Hz, 2 H), 3.85 (s, 3 H), 4.10 (q, J=7.0 Hz, 2 H), 6.84 (dd, J=8.2, 1.6 Hz, 1 H), 7.14 - 7.43 (m, 3 H), 8.31 (s, 1 H).

[0721]

(2) 1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazole-4-carbaldehyde

A solution (15 mL) of methyl 1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazole-4-carboxylate (4.4 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (35 mL) of lithium aluminum hydride (0.61 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr, the mixture was ice-cooled again, and water (1.6 mL), 1N aqueous sodium hydroxide solution (8.0 mL) and water (1.6 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (3.5 g) of 1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazole-4-methanol as a pale-yellow oil. This was dissolved in toluene (100 mL), manganese dioxide (4.0 g) was added, and the mixture was heated under reflux with a Dean-Stark trap for 1 hr. The reaction mixture was allowed to cool to room temperature, manganese dioxide was collected by filtration, and the solvent

was evaporated under reduced pressure to give the title object compound (3.4 g, 87%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.29 - 1.50 (m, 6 H), 2.99 (q, J=7.5 Hz, 2 H), 4.11 (q, J=7.0 Hz, 2 H), 6.88 (ddd, J=8.2, 2.4, 0.8 Hz, 1 H), 7.15 - 7.45 (m, 3 H), 8.32 (s, 1 H), 10.00 (s, 1 H).

[0722]

(3) cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methanol

To a solution (20 mL) of 1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazole-4-carbaldehyde (1.7 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added dropwise under ice-cooling cyclohexylmagnesium bromide (12.0 mL, 1M tetrahydrofuran solution). After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (2.2 g, 96%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.79 - 1.97 (m, 18 H), 2.71 (q, J=7.5 Hz, 2 H), 4.07 - 4.21 (m, 2 H), 4.44 (dd, J=7.3, 2.6 Hz, 1 H), 6.77 (dd, J=7.9, 2.1 Hz, 1 H), 7.13 - 7.37 (m, 3 H), 7.78 (s, 1 H).

[0723]

(4) 3-[{[4-({cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (10 mL) of cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methanol (0.60 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added at room temperature thionyl chloride (0.24 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (15 mL)

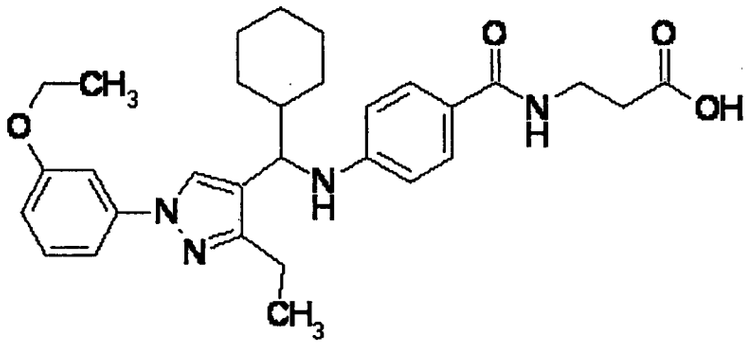
was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (10.0 mL), sodium iodide (0.27 g), sodium carbonate (0.29 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.45 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.7 g) as a pale-yellow oil. This was dissolved in ethanol (3.0 mL), 1N aqueous sodium hydroxide solution (3.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (3.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.66 g, 69%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 2.30 (m, 17 H), 2.60 - 2.75 (m, 4 H), 3.06 (s, 3 H), 3.72 (t, J=6.4 Hz, 1 H), 4.08 (q, J=6.9 Hz, 2 H), 4.22 (d, J=5.7 Hz, 1 H), 6.50 (d, J=8.7 Hz, 2 H), 6.74 (dd, J=8.7, 1.9 Hz, 1 H), 7.09 - 7.34 (m, 5 H), 7.64 (s, 1 H).

[0724]

Example 84

3-({[4-({cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0725]



[0726]

To a solution (10 mL) of cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methanol (0.60 g) synthesized in Example 83(3) in tetrahydrofuran was added at room temperature thionyl chloride (0.24 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (15 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (10.0 mL), sodium iodide (0.27 g), sodium carbonate (0.29 g) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.43 g) synthesized in Example 1(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-({[4-({cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoate (0.6 g) as a pale-yellow oil. This was dissolved in ethanol (3.0 mL), 1N aqueous sodium hydroxide solution (3.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (3.0 mL) was added to the

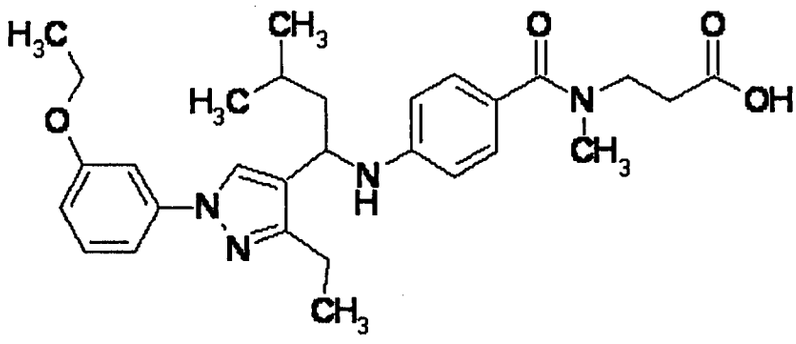
residue. The precipitate was washed with water to give the title object compound (0.59 g, 63%) as a colorless solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 - 2.00 (m, 17 H), 2.56 - 2.81 (m, 4 H), 3.64 (q, J=5.8 Hz, 2 H), 4.06 (q, J=7.0 Hz, 2 H), 4.24 (d, J=6.0 Hz, 1 H), 6.50 (d, J=8.7 Hz, 2 H), 6.54 - 6.62 (m, 1 H), 6.73 (dd, J=7.7, 2.1 Hz, 1 H), 7.07 - 7.32 (m, 3 H), 7.53 (d, J=8.9 Hz, 2 H), 7.63 (s, 1 H).

[0727]

Example 85

3-[{[4-({1-[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]-3-methylbutyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0728]



[0729]

(1) 1-[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]-3-methylbutan-1-ol

To a solution (20 mL) of 1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazole-4-carbaldehyde (1.7 g) synthesized in Example 83(2) in tetrahydrofuran was added dropwise under ice-cooling, isobutylmagnesium bromide (12.0 mL, 1M tetrahydrofuran solution). After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (1.4 g, 67%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 (dd, J=6.4, 2.4 Hz, 6 H), 1.18 - 1.90 (m, 9 H), 2.75 (q, J=7.6 Hz, 2 H), 4.09 (q, J=7.0 Hz, 2 H), 4.81 (d, J=3.6 Hz, 1 H), 6.77 (ddd, J=8.1, 2.4, 0.9 Hz, 1 H), 7.11 - 7.38 (m, 3 H), 7.79 (s, 1 H).

[0730]

(2) 3-[{[4-({1-[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]-3-methylbutyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (10 mL) of 1-[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]-3-methylbutan-1-ol (0.71 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added at room temperature thionyl chloride (0.39 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (15 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (15.0 mL), sodium iodide (0.53 g), sodium carbonate (0.35 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.59 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({1-[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]-3-methylbutyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.55 g) as a pale-yellow oil. This was dissolved in ethanol (3.0 mL), 1N aqueous sodium hydroxide solution (3.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (3.0 mL) was added to the residue. The precipitate was washed with water to give the

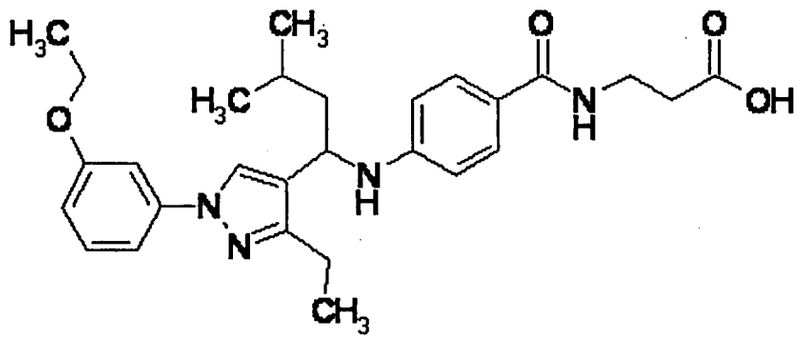
title object compound (0.46 g, 39%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.89 - 2.00 (m, 15 H), 2.56 - 2.82 (m, 4 H), 3.06 (s, 3 H), 3.72 (t, J=6.2 Hz, 2 H), 4.08 (q, J=6.8 Hz, 2 H), 4.46 (t, J=6.8 Hz, 1 H), 6.55 (d, J=7.2 Hz, 2 H), 6.75 (dd, J=8.0, 1.5 Hz, 1 H), 7.05 - 7.38 (m, 5 H), 7.72 (br. s., 1 H).

[0731]

Example 86

3-({[4-({1-[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]-3-methylbutyl}amino)phenyl]carbonyl}amino)propanoic acid

[0732]



[0733]

To a solution (10 mL) of 1-[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]-3-methylbutan-1-ol (0.71 g) synthesized in Example 85(1) in tetrahydrofuran was added at room temperature thionyl chloride (0.39 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (15 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (15.0 mL), sodium iodide (0.53 g), sodium carbonate (0.35 g) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.55 g) synthesized in Example 1(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the

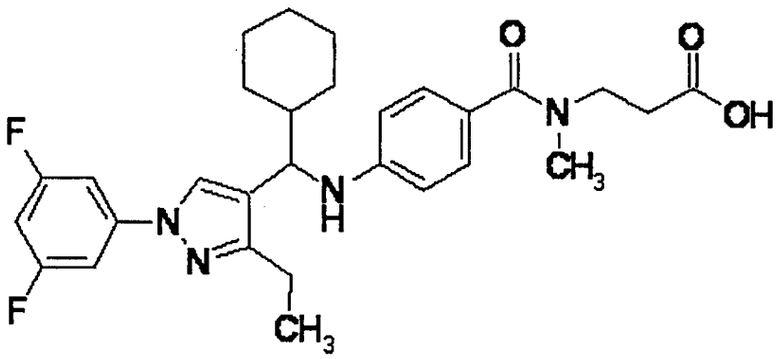
reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-({[4-({1-[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]-3-methylbutyl}amino)phenyl]carbonyl}amino)propanoate (0.56 g) as a pale-yellow oil. This was dissolved in ethanol (3.0 mL), 1N aqueous sodium hydroxide solution (3.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (3.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.54 g, 47%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 - 1.10 (m, 6 H), 1.32 (t, J=7.6 Hz, 3 H), 1.41 (t, J=7.0 Hz, 3 H), 1.57 - 1.87 (m, 3 H), 2.58 - 2.80 (m, 4 H), 3.67 (q, J=5.9 Hz, 2 H), 4.07 (q, J=6.8 Hz, 2 H), 4.48 (t, J=6.6 Hz, 1 H), 4.75 (br. s., 1 H), 6.53 (d, J=8.7 Hz, 2 H), 6.66 (t, J=5.9 Hz, 1 H), 6.74 (dd, J=8.1, 1.7 Hz, 1 H), 7.07 - 7.33 (m, 3 H), 7.57 (d, J=8.7 Hz, 2 H), 7.68 (s, 1 H).

[0734]

Example 87

3-[{[4-({cyclohexyl[1-(3,5-difluorophenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0735]




[0736]

(1) methyl 1-(3,5-difluorophenyl)-3-methyl-1H-pyrazole-4-

carboxylate

A mixture of methyl 3-oxopentanoate (5.2 g) and dimethylformamide dimethylacetal (5.6 mL) was stirred at 100°C overnight, and the mixture was allowed to cool to room temperature. Ethanol (100 mL) and 3,5-difluorophenylhydrazine hydrochloride (7.9 g) were added to the reaction mixture, and the mixture was further stirred at 100°C for 15 hr. After allowing to cool, ethanol was evaporated under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:10, volume ratio) to give the title object compound (6.5 g, 62%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.21 (t, J=7.4 Hz, 3 H), 3.03 (q, J=7.4 Hz, 2 H), 3.87 (s, 3 H), 6.87 - 7.11 (m, 3 H), 8.02 (s, 1 H).

[0737]

(2) 1-(3,5-difluorophenyl)-3-methyl-1H-pyrazole-4-carbaldehyde

A solution (35 mL) of methyl 1-(3,5-difluorophenyl)-3-methyl-1H-pyrazole-4-carboxylate (6.5 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (65 mL) of lithium aluminum hydride (0.94 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr. The mixture was ice-cooled again, and water (2.5 mL), 1N aqueous sodium hydroxide solution (12.5 mL) and water (2.5 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (3.3 g) of 1-(3,5-difluorophenyl)-3-methyl-1H-pyrazole-4-methanol as a pale-yellow oil. This was dissolved in toluene (100 mL), manganese dioxide (6.0 g) was added, and the mixture was heated under reflux with a Dean-Stark trap for 1 hr. The

reaction mixture was allowed to cool to room temperature, manganese dioxide was collected by filtration, and the solvent was evaporated under reduced pressure to give the title object compound (3.1 g, 51%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.25 (t, J=7.6 Hz, 3 H), 3.03 (q, J=7.6 Hz, 2 H), 6.85 - 7.11 (m, 3 H), 8.07 (s, 1 H), 9.99 (s, 1 H).

[0738]

(3) cyclohexyl[1-(3,5-difluorophenyl)-3-methyl-1H-pyrazol-4-yl]methanol

To a solution (10 mL) of 1-(3,5-difluorophenyl)-3-methyl-1H-pyrazole-4-carbaldehyde (1.5 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added dropwise under ice-cooling cyclohexylmagnesium bromide (12.0 mL, 1M tetrahydrofuran solution). After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (1.9 g, quantitative) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.26 (t, J=7.2 Hz, 3 H), 1.32 - 2.14 (m, 12 H), 2.78 (q, J=7.2 Hz, 2 H), 4.35 (dd, J=8.2, 2.9 Hz, 1 H), 6.80 - 7.12 (m, 3 H), 7.62 (s, 1 H).

[0739]

(4) 3-[{[4-({cyclohexyl[1-(3,5-difluorophenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (15 mL) of cyclohexyl[1-(3,5-difluorophenyl)-3-methyl-1H-pyrazol-4-yl]methanol (0.96 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added at room temperature thionyl chloride (0.40 mL). The reaction mixture was stirred at room temperature for 30 min

and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (10 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (15.0 mL), sodium iodide (0.68 g), sodium carbonate (0.48 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.75 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[1-(3,5-difluorophenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.90 g) as a pale-yellow oil. This was dissolved in ethanol (3.0 mL), 1N aqueous sodium hydroxide solution (3.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (3.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.70 g, 44%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 2.08 (m, 14 H), 2.59 - 2.89 (m, 4 H), 3.08 (s, 3 H), 3.73 (t, J=6.5 Hz, 2 H), 4.19 (d, J=6.8 Hz, 1 H), 6.53 (d, J=8.5 Hz, 2 H), 6.77 - 7.30 (m, 5 H), 7.52 (s, 1 H).

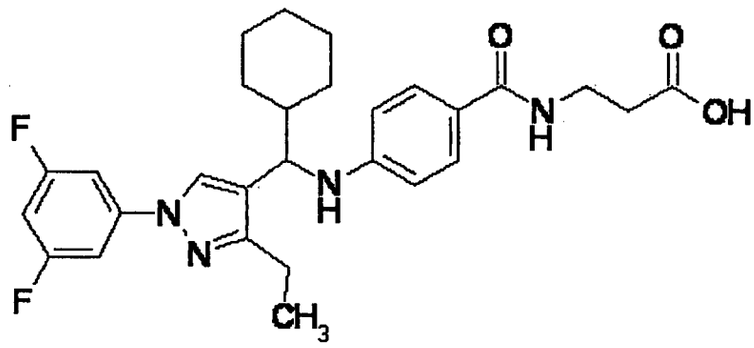
[0740]

Example 88

3-({[4-({cyclohexyl[1-(3,5-difluorophenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0741]

300



[0742]

To a solution (15 mL) of cyclohexyl[1-(3,5-difluorophenyl)-3-methyl-1H-pyrazol-4-yl]methanol (0.96 g) synthesized in Example 87(3) in tetrahydrofuran was added at room temperature thionyl chloride (0.40 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (10 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (15.0 mL), sodium iodide (0.68 g), sodium carbonate (0.48 g) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.70 g) synthesized in Example 1(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-({[4-({cyclohexyl[1-(3,5-difluorophenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)propanoate (0.80 g) as a pale-yellow oil. This was dissolved in ethanol (3.0 mL), 1N aqueous sodium hydroxide solution (3.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (3.0 mL) was added to the

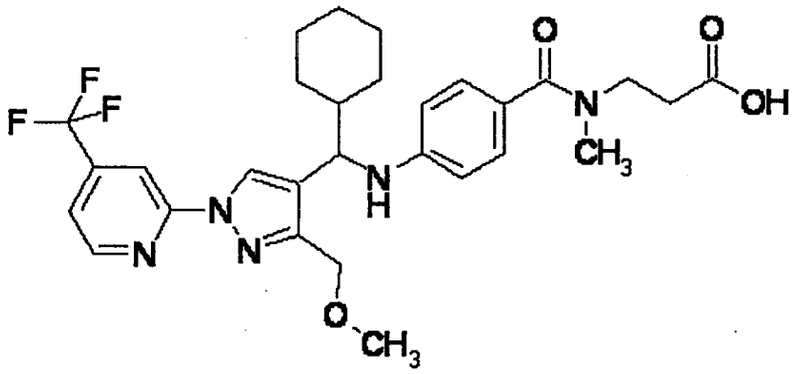
residue. The precipitate was washed with water to give the title object compound (0.50 g, 33%) as a colorless solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 (t, J=7.5 Hz, 3 H), 1.06 - 2.08 (m, 11 H), 2.65 (t, J=5.7 Hz, 2 H), 2.78 (q, J=7.5 Hz, 2 H), 3.67 (q, J=7.0 Hz, 2 H), 4.20 (d, J=6.8 Hz, 1 H), 6.52 (d, J=8.7 Hz, 2 H), 6.57 - 6.68 (m, 1 H), 6.77 - 7.10 (m, 3 H), 7.51 (s, 1 H), 7.55 (d, J=8.7 Hz, 2 H).

[0743]

Example 89

3-[({4-[(cyclohexyl{3-(methoxymethyl)-1-[4-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0744]



[0745]

(1) methyl 3-(methoxymethyl)-1-[4-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate

To a solution of methyl 3-(methoxymethyl)-1H-pyrazole-4-carboxylate (1.8 g) synthesized in Example 37(1) in N,N-dimethylformamide (20 mL) were added 2-chloro-4-trifluoromethylpyridine (2.0 g) and potassium carbonate (2.3 g), and the mixture was stirred at 100°C overnight. The reaction mixture was allowed to cool to room temperature and filtered through celite, water was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4,

volume ratio) to give the title object compound (0.62 g, 18%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.54 (s, 3 H), 3.89 (s, 3 H), 4.83 (s, 2 H), 7.47 (dd, J=5.1, 0.9 Hz, 1 H), 8.31 (s, 1 H), 8.61 (d, J=5.1 Hz, 1 H), 9.04 (s, 1 H).

[0746]

(2) 3-(methoxymethyl)-1-[4-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde

A solution (2 mL) of methyl 3-(methoxymethyl)-1-[4-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate (0.62 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (5 mL) of lithium aluminum hydride (0.10 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr. The mixture was ice-cooled again, and water (0.2 mL), 1N aqueous sodium hydroxide solution (1.0 mL) and water (0.2 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (0.53 g) of 3-(methoxymethyl)-1-[4-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-methanol as a pale-yellow oil. This was dissolved in toluene (30 mL), manganese dioxide (2.0 g) was added, and the mixture was heated under reflux with a Dean-Stark trap for 1 hr. The reaction mixture was allowed to cool to room temperature, and manganese dioxide was collected by filtration. The solvent was evaporated under reduced pressure to give the title object compound (0.59 g, quantitative) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.53 (s, 3 H), 4.83 (s, 2 H), 7.50 (d, J=4.9 Hz, 1 H), 8.31 (s, 1 H), 8.63 (d, J=5.1 Hz, 1 H), 9.09 (s, 1 H), 10.10 (s, 1 H).

[0747]

(3) cyclohexyl{3-(methoxymethyl)-1-[4-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol

To a solution (10 mL) of 3-(methoxymethyl)-1-[4-

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(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde (0.59 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added dropwise under ice-cooling cyclohexylmagnesium bromide (4.0 mL, 1M tetrahydrofuran solution). After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (0.23 g, 30%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.96 (m, 12 H), 3.45 (s, 3 H), 4.43 (d, J=7.7 Hz, 1 H), 4.58 - 4.65 (m, 2 H), 7.38 (d, J=0.9 Hz, 1 H), 8.15 - 8.60 (m, 3 H).

[0748]

(4) 3-[({4-[(cyclohexyl{3-(methoxymethyl)-1-[4-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

To a solution (5 mL) of cyclohexyl{3-(methoxymethyl)-1-[4-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.23 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added at room temperature thionyl chloride (0.10 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (5 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (5.0 mL), sodium iodide (0.14 g), sodium carbonate (0.10 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.17 g) synthesized in Example 2(2) were added, and the mixture was

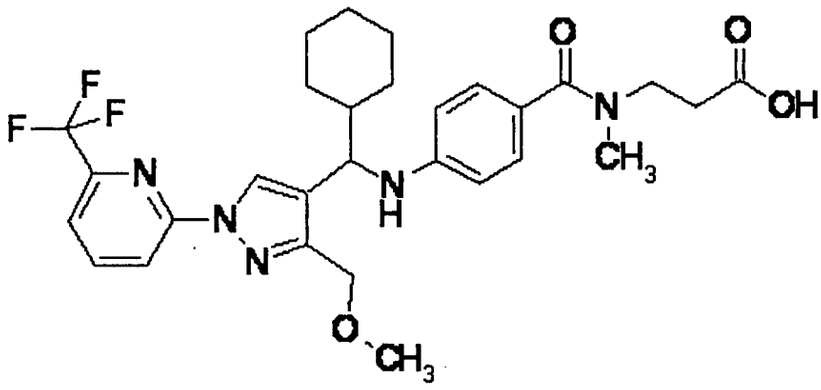
stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[({4-[(cyclohexyl{3-(methoxymethyl)-1-[4-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate (0.10 g) as a pale-yellow oil. This was dissolved in ethanol (1.0 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.04 g, 10%) as a pale-yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 2.18 (m, 11 H), 2.70 (t, J=6.3 Hz, 2 H), 3.06 (s, 3 H), 3.42 (s, 3 H), 3.71 (t, J=6.3 Hz, 2 H), 4.36 (d, J=7.2 Hz, 1 H), 4.57 (d, J=2.1 Hz, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 7.24 (d, J=8.7 Hz, 2 H), 7.37 (d, J=5.3 Hz, 1 H), 8.16 (s, 1 H), 8.36 (s, 1 H), 8.53 (d, J=5.3 Hz, 1 H).

[0749]

Example 90

3-[({4-[(cyclohexyl{3-(methoxymethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[0750]



[0751]

(1) methyl 3-(methoxymethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate

To a solution of methyl 3-(methoxymethyl)-1H-pyrazole-4-carboxylate (5.1 g) synthesized in Example 37(1) in N,N-dimethylformamide (70 mL) were added 2-chloro-6-trifluoromethylpyridine (5.0 g) and potassium carbonate (6.2 g), and the mixture was stirred at 100°C overnight. The reaction mixture was allowed to cool to room temperature and filtered through celite, water was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (6.5 g, 69%) as colorless crystals.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.54 (s, 3 H), 3.89 (s, 3 H), 4.83 (s, 2 H), 7.62 (d, J=7.2 Hz, 1 H), 8.00 - 8.02 (m, 1 H), 8.25 - 8.30 (m, 1 H), 9.06 (s, 1 H).

[0752]

(2) 3-(methoxymethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde

A solution (10 mL) of methyl 3-(methoxymethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carboxylate (6.5 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (25 mL) of lithium aluminum hydride (0.79 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr. The mixture was ice-cooled again, and water (2.0 mL), 1N aqueous sodium hydroxide solution (10.0 mL) and water (2.0 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (6.0 g) of 3-(methoxymethyl)-1-[6-

(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-methanol as a pale-yellow oil. This was dissolved in toluene (100 mL), manganese dioxide (3.0 g) was added, and the mixture was heated under reflux with a Dean-Stark trap for 1 hr. The reaction mixture was allowed to cool to room temperature, and manganese dioxide was collected by filtration. The solvent was evaporated under reduced pressure to give the title object compound (5.3 g, 90%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.53 (s, 3 H), 4.83 (s, 2 H), 7.66 (d, J=7.5 Hz, 1 H), 8.05 - 8.08 (m, 1 H), 8.27 (d, J=8.3 Hz, 1 H), 9.13 (s, 1 H), 10.10 (s, 1 H).

[0753]

(3) cyclohexyl{3-(methoxymethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol

To a solution (100 mL) of 3-(methoxymethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]-1H-pyrazole-4-carbaldehyde (5.3 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added dropwise under ice-cooling cyclohexylmagnesium bromide (25.0 mL, 1M tetrahydrofuran solution). After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (4.6 g, 67%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 2.22 (m, 11 H), 2.95 (d, J=6.0 Hz, 1 H), 3.45 (s, 3 H), 4.44 (dd, J=7.7, 6.0 Hz, 1 H), 4.50 - 4.65 (m, 2 H), 7.53 (d, J=7.0 Hz, 1 H), 7.93 - 8.00 (m, 1 H), 8.14 (d, J=8.3 Hz, 1 H), 8.45 (s, 1 H).

[0754]

(4) 3-[({4-[(cyclohexyl{3-(methoxymethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

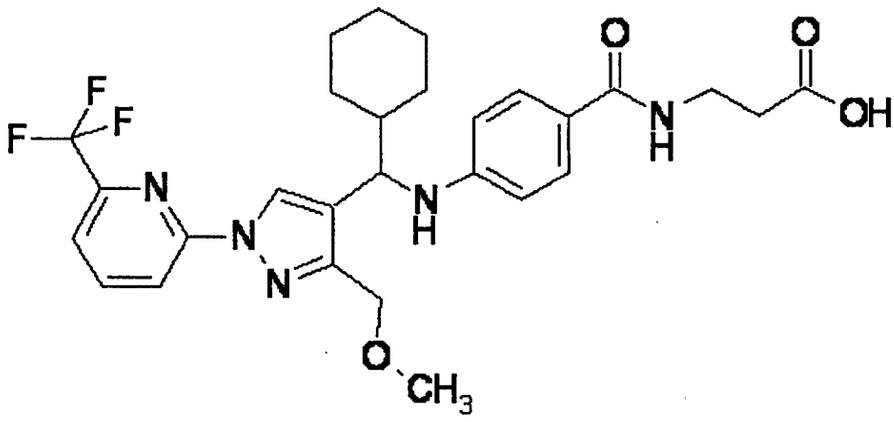
To a solution (5 mL) of cyclohexyl{3-(methoxymethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.50 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added at room temperature thionyl chloride (0.15 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (5 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (5.0 mL), sodium iodide (0.37 g), sodium carbonate (0.26 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.34 g) synthesized in Example 2(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[({4-[(cyclohexyl{3-(methoxymethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate (0.08 g) as a pale-yellow oil. This was dissolved in ethanol (3.0 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.06 g, 7%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 2.19 (m, 11 H), 2.73 (br. s., 2 H), 3.08 (s, 3 H), 3.41 (s, 3 H), 3.72 (t, J=6.2 Hz, 2 H), 4.36 (d, J=8.0 Hz, 1 H), 4.57 (d, J=2.1 Hz, 2 H), 6.58 (d, J=8.7 Hz, 2 H), 7.20 - 7.30 (m, 2 H), 7.51 - 8.12 (m, 3 H), 8.40 (s, 1 H).

[0755]

Example 91

3-[({4-[(cyclohexyl{3-(methoxymethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[0756]



[0757]

To a solution (5 mL) of cyclohexyl{3-(methoxymethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methanol (0.50 g) synthesized in Example 90(3) in tetrahydrofuran was added at room temperature thionyl chloride (0.15 mL). The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (5 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (5.0 mL), sodium iodide (0.37 g), sodium carbonate (0.26 g) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.32 g) synthesized in Example 1(2) were added, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column

chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[({4-[(cyclohexyl{3-(methoxymethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoate (0.07 g) as a pale-yellow oil. This was dissolved in ethanol (3.0 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.06 g, 8%) as a colorless solid.

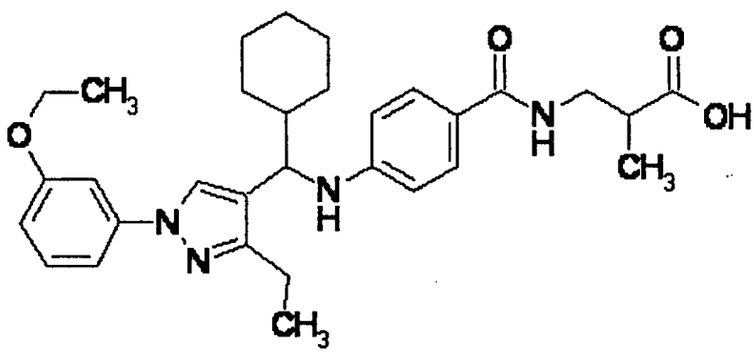
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.87 - 2.17 (m, 11 H), 2.67 (t, J=5.7 Hz, 2 H), 3.41 (s, 3 H), 3.56 - 3.77 (m, 2 H), 4.38 (d, J=7.6 Hz, 1 H), 4.56 (d, J=2.3 Hz, 2 H), 6.47 - 6.71 (m, 3 H), 7.46 - 8.11 (m, 5 H), 8.40 (s, 1 H).

[0758]

Example 92

3-({[4-({cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)-2-methylpropanoic acid

[0759]



[0760]

(1) methyl 4-({cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)benzoate

To a solution (5 mL) of cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methanol (0.64 g) synthesized in Example 83(3) in tetrahydrofuran was added at room temperature thionyl chloride (0.22 mL). The reaction mixture was stirred at room

temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (10 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (10.0 mL), sodium iodide (0.44 g), sodium carbonate (0.30 g) and methyl 4-aminobenzoate (0.35 g) were added, and the mixture was stirred at 70°C overnight. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (0.34 g, 38%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.76 - 1.85 (m, 17 H), 2.63 - 2.82 (m, 2 H), 3.82 (s, 3 H), 4.02 - 4.11 (m, 2 H), 4.27 (br. s., 1 H), 6.51 (d, J=8.9 Hz, 2 H), 6.75 (dd, J=2.4, 0.9 Hz, 1 H), 7.09 - 7.26 (m, 3 H), 7.64 (s, 1 H), 7.80 (d, J=8.9 Hz, 2 H).

[0761]

(2) 4-({cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)benzoic acid

To a solution of methyl 4-({cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)benzoate (0.34 g) synthesized in the above-mentioned (1) in ethanol (6.0 mL) was added 1N aqueous sodium hydroxide solution (6.0 mL), and the mixture was stirred at 60°C for 6 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (8.0 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a crude product (0.33 g, quantitative) of the title object compound as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 2.00 (m, 17 H), 2.72 (q, J=7.5 Hz, 2 H), 3.99 - 4.11 (m, 2 H), 4.28 (d, J=5.8 Hz, 1 H), 6.52 (d, J=8.9 Hz, 2 H), 6.74 (ddd, J=8.1, 2.5, 0.8 Hz, 1 H), 7.10 - 7.25 (m, 3 H), 7.65 (s, 1 H), 7.84 (d, J=8.9 Hz, 2 H).

[0762]

(3) 3-({[4-({cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)-2-methylpropanoic acid

4-({Cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)benzoic acid (0.18 g) synthesized in the above-mentioned (2) was dissolved in N,N-dimethylformamide (3 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.11 g), 1-hydroxybenzotriazole·monohydrate (0.09 g) and methyl 3-amino-2-methylpropanoate (0.07 g) were added at room temperature, and the mixture was stirred overnight. Water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give methyl 3-({[4-({cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)-2-methylpropanoate (0.03 g) as a yellow oil. This was dissolved in ethanol (2.0 mL), 1N aqueous sodium hydroxide solution (0.5 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (0.5 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.02 g, 9%) as a colorless solid.

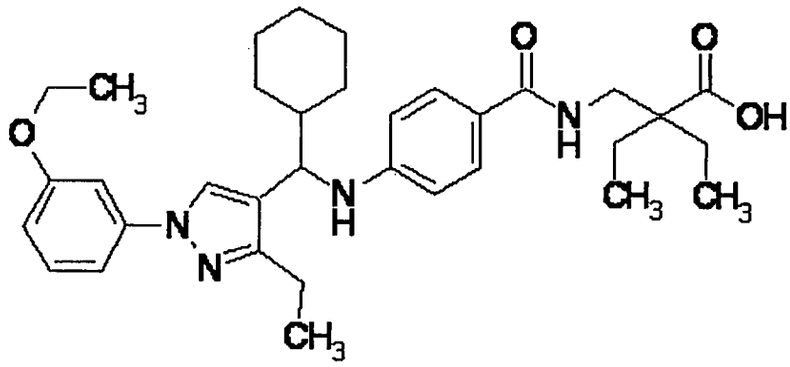
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 2.00 (m, 20 H), 2.62 - 2.91 (m, 3 H), 3.59 - 3.75 (m, 2 H), 4.07 (q, J=6.8 Hz, 2 H), 4.24 (d, J=6.0 Hz, 1 H), 6.43 - 6.59 (m, 3 H), 6.74 (dd, J=8.1, 2.4 Hz, 1 H), 7.08 - 7.66 (m, 6 H).

[0763]

Example 93

2-[({[4-({cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)methyl]-2-ethylbutanoic acid

[0764]



[0765]

4-({Cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)benzoic acid (0.18 g) synthesized in Example 92(2) was dissolved in N,N-dimethylformamide (3 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.11 g), 1-hydroxybenzotriazole·monohydrate (0.09 g), ethyl 2-(aminomethyl)-2-ethylbutanoate hydrochloride (0.12 g) and triethylamine (0.09 mL) were added at room temperature, and the mixture was stirred overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give ethyl 2-[({[4-({cyclohexyl[1-(3-ethoxyphenyl)-3-ethyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}amino)methyl]-2-ethylbutanoate (0.18 g) as a yellow oil. This was dissolved in ethanol (2.0 mL), 1N aqueous sodium hydroxide solution (2.0 mL) was added at room temperature, and the mixture was stirred at 60°C overnight. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (2.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.17 g, 74%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (t, J=7.4 Hz, 6 H), 1.00 -

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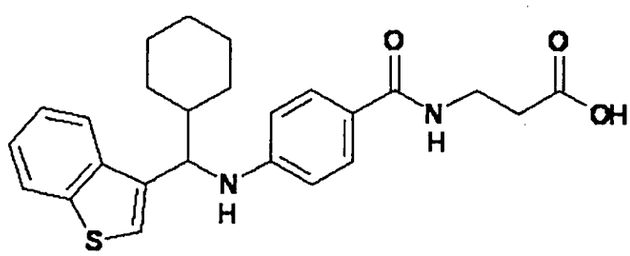
1.99 (m, 21 H), 2.72 (q, J=7.5 Hz, 2 H), 3.62 (d, J=6.2 Hz, 2 H), 4.07 (q, J=7.0 Hz, 2 H), 4.24 (d, J=6.0 Hz, 1 H), 6.38 - 6.47 (m, 1 H), 6.51 (d, J=8.9 Hz, 2 H), 6.73 (ddd, J=7.1, 1.5, 1.2 Hz, 1 H), 7.09 - 7.24 (m, 3 H), 7.54 (d, J=8.9 Hz, 2 H), 7.63 (s, 1 H).

[0766]

Example A1

3-{[(4-{[1-benzothiophen-3-yl(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0767]




[0768]

(1) 1-benzothiophen-3-yl(cyclohexyl)methanol

To a solution (40 mL) of 1-benzothiophene-3-carbaldehyde (2.25 g) in tetrahydrofuran was added dropwise 1.0M cyclohexylmagnesium bromide tetrahydrofuran solution (20.9 mL) at 0°C, and the mixture was stirred for 1.5 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=3:17, volume ratio) to give the title object compound (2.37 g, 69%) as an orange oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 1.31 (m, 5 H), 1.43 - 1.52 (m, 1 H), 1.60 - 1.73 (m, 2 H), 1.74 - 1.83 (m, 1 H), 1.83 - 1.96 (m, 2 H), 1.97 - 2.05 (m, 1 H), 4.83 (dd, J=6.8, 3.2 Hz, 1 H), 7.30 - 7.40 (m, 3 H), 7.82 - 7.93 (m, 2 H).

[0769]

(2) 3-[chloro(cyclohexyl)methyl]-1-benzothiophene

To a solution of 1-benzothiophen-3-yl(cyclohexyl)methanol (2.32 g) synthesized above in toluene (25 mL) was added dropwise thionyl chloride (824 μL), and the mixture was stirred at room temperature for 4 hr. The reaction mixture was poured into ice-cooled saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (2.42 g, 97%) as an orange oil. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.34 (m, 5 H), 1.46 - 1.56 (m, 1 H), 1.60 - 1.72 (m, 2 H), 1.76 - 1.86 (m, 1 H), 2.10 - 2.28 (m, 2 H), 5.03 (d, J=8.1 Hz, 1 H), 7.32 - 7.43 (m, 3 H), 7.82 - 7.93 (m, 2 H).

[0770]

(3) 4-{[1-benzothiophen-3-yl(cyclohexyl)methyl]amino}benzoic acid

To a mixture of 3-[chloro(cyclohexyl)methyl]-1-benzothiophene (2.42 g) synthesized above, methyl 4-aminobenzoate (2.77 g), sodium iodide (2.74 g) and N,N-dimethylacetamide (50 mL) was added sodium carbonate (1.94 g), and the mixture was stirred under argon atmosphere at 100°C overnight. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:3, volume ratio) to give a pale-yellow oil. To a mixture of the obtained oil, tetrahydrofuran (20 mL) and ethanol (20 mL) was added 1N aqueous sodium hydroxide solution (20 mL), and the mixture was stirred overnight with heating under reflux. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in water (40 mL), and 1N hydrochloric acid (20 mL) was added at 0°C. The resulting precipitate was collected by filtration to give

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the title object compound (1.80 g, 54%) as a white solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.35 (m, 5 H), 1.60 - 2.03 (m, 6 H), 4.69 (d, J=5.7 Hz, 1 H), 6.43 - 6.53 (m, 2 H), 7.22 (s, 1 H), 7.32 - 7.47 (m, 2 H), 7.73 - 7.91 (m, 4 H).

[0771]

(4) 3-{[(4-{[1-benzothiophen-3-yl(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of 4-{[1-benzothiophen-3-yl(cyclohexyl)methyl]amino}benzoic acid (250 mg) synthesized above, β-alanine ethyl ester hydrochloride (126 mg), 1-hydroxybenzotriazole·monohydrate (126 mg), triethylamine (114 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (157 mg), and the mixture was stirred at room temperature for 2 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give a pale-yellow oil. To a mixture of the obtained oil, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1 mL), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in water (10 mL), and 1N hydrochloric acid (1 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (201 mg, 67%) as a white solid.

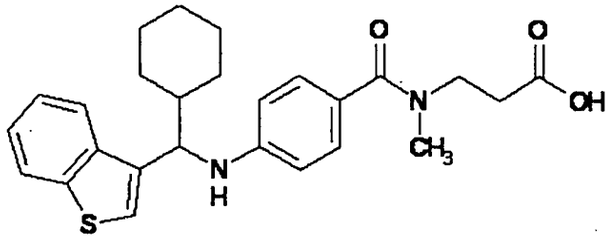
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 1.32 (m, 5 H), 1.57 - 1.81 (m, 4 H), 1.81 - 1.99 (m, 2 H), 2.57 (t, J=5.7 Hz, 2 H), 3.53 - 3.63 (m, 2 H), 4.63 (d, J=5.7 Hz, 1 H), 6.42 (d, J=8.7 Hz, 2 H), 6.62 (t, J=6.1 Hz, 1 H), 7.18 (s, 1 H), 7.31 - 7.46 (m, 4 H), 7.80 - 7.89 (m, 2 H).

[0772]

Example A2

3-{[(4-{[1-benzothiophen-3-yl(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[0773]



[0774]

Using 4-{[1-benzothiophen-3-yl(cyclohexyl)methyl]amino}benzoic acid (250 mg) synthesized in Example A1(3) and ethyl 3-(methylamino)propanoate (108 mg) and in the same manner as in Example A1(4), the title object compound (220 mg, 71%) was obtained as a white solid.

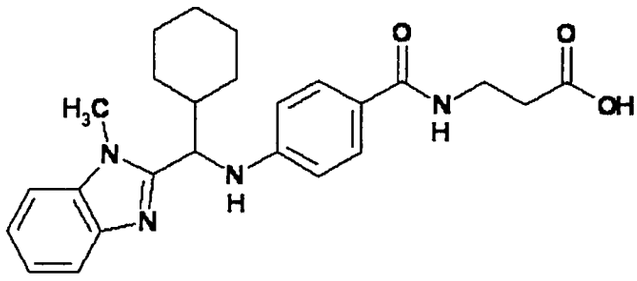
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.34 (m, 5 H), 1.61 - 1.83 (m, 4 H), 1.83 - 2.00 (m, 2 H), 2.67 (t, J=6.4 Hz, 2 H), 3.02 (s, 3 H), 3.69 (t, J=6.4 Hz, 2 H), 4.64 (d, J=5.7 Hz, 1 H), 6.45 (d, J=8.7 Hz, 2 H), 7.19 (d, J=8.7 Hz, 2 H), 7.21 (s, 1 H), 7.33 - 7.45 (m, 2 H), 7.82 - 7.91 (m, 2 H).

[0775]

Example A3

3-{[(4-{[cyclohexyl(1-methyl-1H-benzimidazol-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0776]



[0777]

(1) cyclohexyl(1-methyl-1H-benzimidazol-2-yl)methanol

Using 1-methyl-1H-benzoimidazole-2-carbaldehyde (1.03 g) and in the same manner as in Example A1(1), the title object compound (0.58 g, 37%) was obtained as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.05 - 1.30 (m, 5 H), 1.36 - 1.46 (m, 1 H), 1.58 - 2.03 (m, 5 H), 3.77 (s, 3 H), 4.65 (d, J=7.2 Hz, 1 H), 7.20 - 7.30 (m, 3 H), 7.65 - 7.73 (m, 1 H).

(2) 2-[chloro(cyclohexyl)methyl]-1-methyl-1H-benzoimidazole

Using cyclohexyl(1-methyl-1H-benzimidazol-2-yl)methanol (0.58 g) synthesized above and in the same manner as in Example A1(2), the title object compound (605 mg, 97%) was obtained as a brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 - 1.45 (m, 5 H), 1.50 - 1.60 (m, 1 H), 1.62 - 1.75 (m, 2 H), 1.81 - 1.92 (m, 1 H), 2.33 - 2.49 (m, 2 H), 3.87 (s, 3 H), 4.88 (d, J=9.9 Hz, 1 H), 7.24 - 7.38 (m, 3 H), 7.74 - 7.79 (m, 1 H).

(3) 4-{[cyclohexyl(1-methyl-1H-benzimidazol-2-yl)methyl]amino}benzoic acid

Using 2-[chloro(cyclohexyl)methyl]-1-methyl-1H-benzoimidazole (605 mg) synthesized above and in the same manner as in Example A1(3), the title object compound (87.0 mg, 10%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 - 1.32 (m, 5 H), 1.39 - 1.51 (m, 1 H), 1.60 - 1.84 (m, 3 H), 2.03 - 2.20 (m, 2 H), 3.90 (s, 3 H), 4.63 - 4.72 (m, 1 H), 5.90 - 6.04 (m, 1 H), 6.69 (d, J=8.7 Hz, 2 H), 7.25 - 7.39 (m, 3 H), 7.73 - 7.81 (m, 1 H), 7.88 (d, J=8.7 Hz, 2 H).

(4) 3-{[(4-{[cyclohexyl(1-methyl-1H-benzimidazol-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

Using 4-{[cyclohexyl(1-methyl-1H-benzimidazol-2-yl)methyl]amino}benzoic acid (78.3 mg) synthesized above and in the same manner as in Example A1(4), the title object compound (39.5 mg, 42%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 - 1.40 (m, 6 H), 1.59 - 1.71 (m, 2 H), 1.71 - 1.84 (m, 1 H), 1.92 - 2.08 (m, 1 H), 2.13 -

2.26 (m, 1 H), 2.71 (t, J=5.3 Hz, 2 H), 3.71 - 3.83 (m, 2 H), 3.93 (s, 3 H), 4.59 - 4.71 (m, 1 H), 6.74 (d, J=8.7 Hz, 2 H), 7.20 - 7.40 (m, 4 H), 7.59 - 7.70 (m, 3 H).

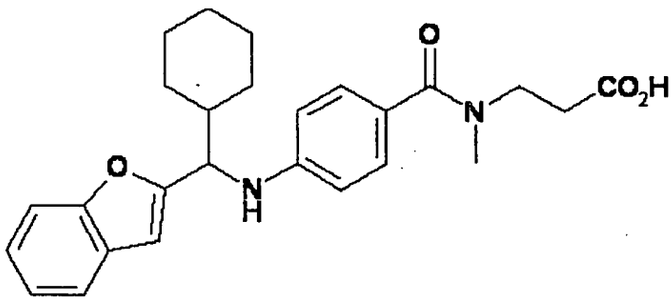
318

[0778]

Example A4

3-{[(4-{[1-benzofuran-2-yl(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[0779]



[0780]

(1) 1-benzofuran-2-yl(cyclohexyl)methanol

Using 1-benzofuran-2-carbaldehyde (2.52 g) and in the same manner as in Example A1(1), the title object compound (2.38 g, 60%) was obtained as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 1.36 (m, 5 H), 1.49 - 1.59 (m, 1 H), 1.61 - 2.03 (m, 6 H), 4.50 - 4.57 (m, 1 H), 6.60 (s, 1 H), 7.16 - 7.29 (m, 2 H), 7.43 - 7.47 (m, 1 H), 7.50 - 7.55 (m, 1 H).

(2) 2-[chloro(cyclohexyl)methyl]-1-benzofuran

Using 1-benzofuran-2-yl(cyclohexyl)methanol (1.20 g) synthesized above and in the same manner as in Example A1(2), the title object compound (1.17 g, 90%) was obtained as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 - 1.38 (m, 5 H), 1.50 - 1.86 (m, 4 H), 2.08 - 2.23 (m, 2 H), 4.78 (d, J=8.1 Hz, 1 H), 6.66 (s, 1 H), 7.12 - 7.32 (m, 2 H), 7.45 - 7.56 (m, 2 H).

(3) 4-{[1-benzofuran-2-yl(cyclohexyl)methyl]amino}benzoic acid

Using 2-[chloro(cyclohexyl)methyl]-1-benzofuran (1.17 g)

synthesized above and in the same manner as in Example A1(3), the title object compound (523 mg, 32%) was obtained as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.05 - 1.38 (m, 5 H), 1.57 - 1.86 (m, 4 H), 1.88 - 2.03 (m, 2 H), 4.41 - 4.50 (m, 1 H), 4.52 - 4.62 (m, 1 H), 6.53 (s, 1 H), 6.60 (d, J=8.9 Hz, 2 H), 7.14 - 7.25 (m, 2 H), 7.41 - 7.50 (m, 2 H), 7.85 (d, J=8.9 Hz, 2 H).

(4) 3-{[(4-{[1-benzofuran-2-yl(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

Using 4-{[1-benzofuran-2-yl(cyclohexyl)methyl]amino}benzoic acid (250 mg) synthesized above and ethyl 3-(methylamino)propanoate (113 mg) and in the same manner as in Example A1(4), the title object compound (226 mg, 73%) was obtained as a pale-red solid.

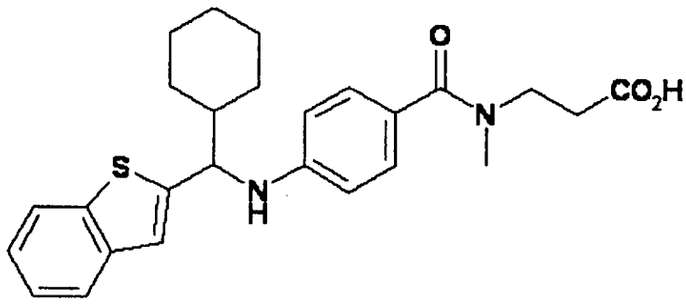
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.98 - 1.29 (m, 5 H), 1.39 - 1.50 (m, 1 H), 1.55 - 1.78 (m, 3 H), 1.83 - 2.03 (m, 2 H), 2.43 - 2.54 (m, 2 H), 2.89 (s, 3 H), 3.51 (t, J=7.3 Hz, 2 H), 4.38 - 4.49 (m, 1 H), 6.46 (d, J=8.1 Hz, 1 H), 6.67 (d, J=8.7 Hz, 2 H), 6.75 (s, 1 H), 7.11 (d, J=8.7 Hz, 2 H), 7.14 - 7.26 (m, 2 H), 7.47 - 7.57 (m, 2 H).

[0781]

Example A5

3-{[(4-{[1-benzothiophen-2-yl(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[0782]




[0783]

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(1) 1-benzothiophen-2-yl(cyclohexyl)methanol

Using 1-benzothiophene-2-carbaldehyde (2.00 g) and in the same manner as in Example A1(1), the title object compound (1.93 g, 64%) was obtained as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 1.35 (m, 5 H), 1.50 - 1.84 (m, 5 H), 1.99 - 2.10 (m, 2 H), 4.70 (dd, J = 7.2, 3.9 Hz, 1 H), 7.15 (s, 1 H), 7.24 - 7.36 (m, 2 H), 7.67 - 7.73 (m, 1 H), 7.77 - 7.83 (m, 1 H).

(2) 2-[chloro(cyclohexyl)methyl]-1-benzothiophene

Using 1-benzothiophen-2-yl(cyclohexyl)methanol (1.93 g) synthesized above and in the same manner as in Example A1(2), the title object compound (1.94 g, 94%) was obtained as a brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 - 1.38 (m, 5 H), 1.50 - 2.01 (m, 5 H), 2.15 - 2.25 (m, 1 H), 4.97 (d, J=7.8 Hz, 1 H), 7.21 (s, 1 H), 7.26 - 7.37 (m, 2 H), 7.66 - 7.73 (m, 1 H), 7.74 - 7.82 (m, 1 H).

(3) 4-{[1-benzothiophen-2-yl(cyclohexyl)methyl]amino}benzoic acid

Using 2-[chloro(cyclohexyl)methyl]-1-benzothiophene (1.93 g) synthesized above and in the same manner as in Example A1(3), the title object compound (719 mg, 27%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.06 - 1.37 (m, 5 H), 1.61 - 1.90 (m, 5 H), 1.91 - 2.04 (m, 1 H), 4.51 - 4.67 (m, 1 H), 6.61 (d, J=8.8 Hz, 2 H), 7.16 (s, 1 H), 7.21 - 7.36 (m, 2 H), 7.67 (d, J=7.0 Hz, 1 H), 7.74 (d, J=7.9 Hz, 1 H), 7.84 (d, J=8.8 Hz, 2 H).

(4) 3-{[(4-{[1-benzothiophen-2-yl(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

Using 4-{[1-benzothiophen-2-yl(cyclohexyl)methyl]amino}benzoic acid (250 mg) synthesized above and ethyl 3-(methylamino)propanoate (108 mg) and in the same manner as in Example A1(4), the title object compound

(277 mg, 90%) was obtained as a white solid.

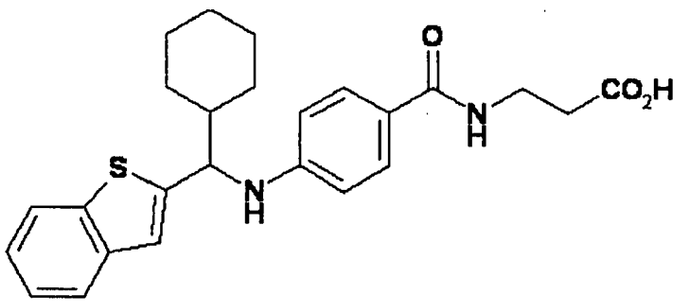
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 1.06 - 1.36 (m, 5 H), 1.62 - 1.87 (m, 5 H), 1.91 - 2.01 (m, 1 H), 2.65 (t, J=6.4 Hz, 2 H), 3.01 (s, 3 H), 3.69 (t, J=6.4 Hz, 2 H), 4.49 (d, J=6.2 Hz, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 7.15 (s, 1 H), 7.18 - 7.35 (m, 4 H), 7.64 - 7.70 (m, 1 H), 7.71 - 7.76 (m, 1 H).

[0784]

Example A6

3-{[(4-{[1-benzothiophen-2-yl(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0785]




[0786]

Using 4-{[1-benzothiophen-2-yl(cyclohexyl)methyl]amino}benzoic acid (250 mg) synthesized in Example A5(3) and in the same manner as in Example A1(4), the title object compound (275 mg, 92%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.06 - 1.35 (m, 5 H), 1.61 - 1.87 (m, 5 H), 1.89 - 2.01 (m, 1 H), 2.60 (t, J=5.7 Hz, 2 H), 3.55 - 3.67 (m, 2 H), 4.50 (d, J=6.2 Hz, 1 H), 6.53 - 6.64 (m, 3 H), 7.14 (s, 1 H), 7.19 - 7.34 (m, 2 H), 7.50 (d, J=8.7 Hz, 2 H), 7.66 (d, J=7.3 Hz, 1 H), 7.72 (d, J=7.9 Hz, 1 H).

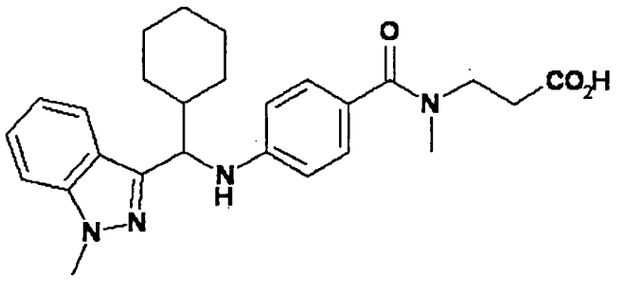
[0787]

Example A7

3-{[(4-{[cyclohexyl(1-methyl-1H-indazol-3-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0788]

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[0789]

(1) cyclohexyl(1-methyl-1H-indazol-3-yl)methanol

Using 1-methyl-1H-indazole-3-carbaldehyde (1.00 g) and in the same manner as in Example A1(1), the title object compound (799 mg, 52%) was obtained as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 - 1.37 (m, 5 H), 1.45 - 1.54 (m, 1 H), 1.60 - 1.82 (m, 3 H), 1.84 - 2.03 (m, 2 H), 2.37 - 2.43 (m, 1 H), 4.02 (s, 3 H), 4.83 - 4.89 (m, 1 H), 7.09 - 7.16 (m, 1 H), 7.31 - 7.41 (m, 2 H), 7.80 (d, J=8.1 Hz, 1 H).

(2)3-[chloro(cyclohexyl)methyl]-1-methyl-1H-indazole

Using cyclohexyl(1-methyl-1H-indazol-3-yl)methanol (799 mg) synthesized above and in the same manner as in Example A1(2), the title object compound (818 mg, 95%) was obtained as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.38 (m, 5 H), 1.40 - 1.50 (m, 1 H), 1.59 - 1.70 (m, 2 H), 1.77 - 1.87 (m, 1 H), 2.18 - 2.40 (m, 2 H), 4.03 (s, 3 H), 5.06 (d, J=8.7 Hz, 1 H), 7.12 - 7.19 (m, 1 H), 7.32 - 7.42 (m, 2 H), 7.87 (d, J=8.1 Hz, 1 H).

(3) 3-{[(4-{[cyclohexyl(1-methyl-1H-indazol-3-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of 3-[chloro(cyclohexyl)methyl]-1-methyl-1H-indazole (465 mg) synthesized above, ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (531 mg) synthesized in Example 2(2), sodium iodide (531 mg) and N,N-dimethylacetamide (10 mL) was added sodium carbonate (375 mg), and the mixture was stirred under argon atmosphere at 100°C overnight. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted

with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=3:2, volume ratio) to give a white solid. To a mixture of the obtained solid, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (356 mg, 45%) as a white solid.

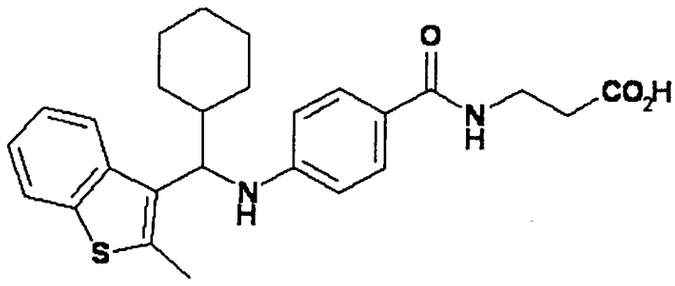
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 - 1.34 (m, 5 H), 1.47 - 1.82 (m, 4 H), 1.89 - 2.10 (m, 2 H), 2.66 (t, J=6.5 Hz, 2 H), 3.03 (s, 3 H), 3.69 (t, J=6.5 Hz, 2 H), 4.01 (s, 3 H), 4.70 (d, J=7.0 Hz, 1 H), 6.60 (d, J=8.6 Hz, 2 H), 7.06 - 7.14 (m, 1 H), 7.20 (d, J=8.6 Hz, 2 H), 7.29 - 7.40 (m, 2 H), 7.74 (d, J=8.1 Hz, 1 H).

[0790]

Example A8

3-{[(4-{[cyclohexyl(2-methyl-1-benzothiophen-3-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0791]




[0792]

(1) 3-bromo-2-methyl-1-benzothiophene

To a solution (50 mL) of 2-methyl-1-benzothiophene (5.00 g) in acetic acid was added dropwise bromine (1.90 mL) at 0°C,

and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, saturated aqueous sodium hydrogen carbonate solution was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (8.02 g, quantitative) as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.56 (s, 3 H), 7.28 - 7.36 (m, 1 H), 7.36 - 7.44 (m, 1 H), 7.67 - 7.75 (m, 2 H).

(2) cyclohexyl(2-methyl-1-benzothiophen-3-yl)methanol

3-Bromo-2-methyl-1-benzothiophene (2.00 g) synthesized above was dissolved in tetrahydrofuran (40 mL), 1.6M n-butyllithium hexane solution (6.63 mL) was added dropwise at -78°C. The mixture was stirred under a nitrogen atmosphere for 10 min, cyclohexanecarbaldehyde (2.50 mL) was added, and the mixture was stirred -78°C for 30 min and at room temperature for 30 min. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=3:17, volume ratio) to give the title object compound (1.95 g, 85%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.42 (m, 5 H), 1.51 - 1.70 (m, 2 H), 1.71 - 1.92 (m, 3 H), 1.97 - 2.13 (m, 1 H), 2.24 - 2.35 (m, 1 H), 2.54 (s, 3 H), 4.74 (dd, J=9.1, 2.2 Hz, 1 H), 7.21 - 7.35 (m, 2 H), 7.71 - 7.77 (m, 1 H), 7.97 - 8.05 (m, 1 H).

(3) 3-[chloro(cyclohexyl)methyl]-2-methyl-1-benzothiophene

Using cyclohexyl(2-methyl-1-benzothiophen-3-yl)methanol (1.95 g) synthesized above and in the same manner as in

Example A1(2), the title object compound (1.98 g, 95%) was obtained as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.70 - 0.85 (m, 1 H), 0.96 - 1.40 (m, 4 H), 1.49 - 1.91 (m, 4 H), 2.24 - 2.32 (m, 1 H), 2.46 - 2.58 (m, 4 H), 4.94 (d, J=10.5 Hz, 1 H), 7.23 - 7.36 (m, 2 H), 7.70 - 7.75 (m, 1 H), 7.99 (d, J=7.5 Hz, 1 H).

(4) 4-{[cyclohexyl(2-methyl-1-benzothiophen-3-yl)methyl]amino}benzoic acid

Using 3-[chloro(cyclohexyl)methyl]-2-methyl-1-benzothiophene (1.98 g) synthesized above and in the same manner as in Example A1(3), the title object compound (1.69 g, 63%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 1.34 (m, 5 H), 1.39 - 1.51 (m, 1 H), 1.62 - 1.71 (m, 2 H), 1.78 - 1.89 (m, 1 H), 1.93 - 2.08 (m, 1 H), 2.09 - 2.20 (m, 1 H), 2.58 (s, 3 H), 4.56 (d, J=8.5 Hz, 1 H), 6.46 (d, J=9.0 Hz, 2 H), 7.21 - 7.36 (m, 2 H), 7.69 - 7.84 (m, 4 H).

(5) 3-{[(4-{[cyclohexyl(2-methyl-1-benzothiophen-3-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

Using 4-{[cyclohexyl(2-methyl-1-benzothiophen-3-yl)methyl]amino}benzoic acid (300 mg) synthesized above and in the same manner as in Example A1(4), the title object compound (323 mg, 91%) was obtained as a white solid.

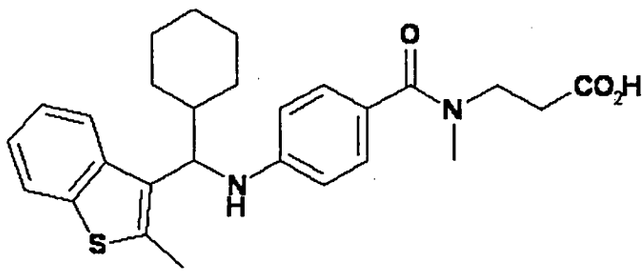
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.34 (m, 5 H), 1.40 - 1.51 (m, 1 H), 1.61 - 1.72 (m, 2 H), 1.78 - 1.88 (m, 1 H), 1.92 - 2.07 (m, 1 H), 2.09 - 2.20 (m, 1 H), 2.53 - 2.65 (m, 5 H), 3.54 - 3.65 (m, 2 H), 4.52 (d, J=8.7 Hz, 1 H), 6.39 - 6.55 (m, 3 H), 7.20 - 7.34 (m, 2 H), 7.39 - 7.48 (m, 2 H), 7.72 (d, J=8.0 Hz, 1 H), 7.81 (d, J=7.6 Hz, 1 H).

[0793]

Example A9

3-{[(4-{[cyclohexyl(2-methyl-1-benzothiophen-3-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0794]



[0795]

Using 4-{[cyclohexyl(2-methyl-1-benzothiophen-3-yl)methyl]amino}benzoic acid (300 mg) synthesized in Example A8(4) and ethyl 3-(methylamino)propanoate (124 mg) and in the same manner as in Example A1(4), the title object compound (312 mg, 85%) was obtained as a white solid.

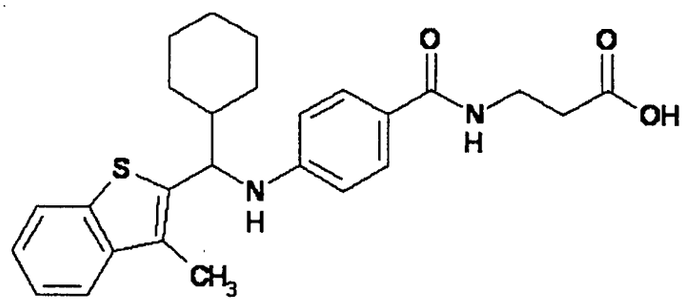
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.35 (m, 5 H), 1.39 - 1.50 (m, 1 H), 1.61 - 1.73 (m, 2 H), 1.78 - 1.88 (m, 1 H), 1.91 - 2.06 (m, 1 H), 2.09 - 2.20 (m, 1 H), 2.57 (s, 3 H), 2.58 - 2.67 (m, 2 H), 2.99 (s, 3 H), 3.67 (t, J=6.4 Hz, 1 H), 4.50 (d, J=8.7 Hz, 1 H), 6.44 (d, J=8.5 Hz, 2 H), 7.17 (d, J=8.5 Hz, 1 H), 7.21 - 7.35 (m, 2 H), 7.73 (d, J=7.2 Hz, 1 H), 7.83 (d, J=7.6 Hz, 1 H).

[0796]

Example A10

3-{[(4-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0797]



[0798]

(1) cyclohexyl(3-methyl-1-benzothiophen-2-yl)methanol

Using 3-methyl-1-benzothiophene-2-carbaldehyde (2.00 g) and in the same manner as in Example A1(1), the title object

compound (1.65 g, 56%) was obtained as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 - 1.36 (m, 5 H), 1.41 - 1.52 (m, 1 H), 1.60 - 1.86 (m, 4 H), 2.01 (d, J=3.3 Hz, 1 H), 2.14 - 2.24 (m, 1 H), 2.37 (s, 3 H), 4.83 (dd, J=8.1, 3.3 Hz, 1 H), 7.27 - 7.39 (m, 2 H), 7.62 - 7.67 (m, 1 H), 7.77 - 7.82 (m, 1 H).

(2) 2-[chloro(cyclohexyl)methyl]-3-methyl-1-benzothiophene

Using cyclohexyl(3-methyl-1-benzothiophen-2-yl)methanol (1.65 g) synthesized above and in the same manner as in Example A1(2), the title object compound (1.68 g, 95%) was obtained as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 - 0.99 (m, 1 H), 1.04 - 1.39 (m, 4 H), 1.56 - 1.71 (m, 3 H), 1.77 - 1.88 (m, 1 H), 1.88 - 2.03 (m, 1 H), 2.32 - 2.45 (m, 4 H), 5.09 (d, J=9.6 Hz, 1 H), 7.29 - 7.39 (m, 2 H), 7.62 - 7.67 (m, 1 H), 7.75 - 7.80 (m, 1 H).

(3) 4-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}benzoic acid

Using 2-[chloro(cyclohexyl)methyl]-3-methyl-1-benzothiophene (1.68 g) synthesized above and in the same manner as in Example A1(3), the title object compound (1.63 g, 71%) was obtained as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 1.34 (m, 5 H), 1.53 - 1.87 (m, 5 H), 2.03 - 2.16 (m, 1 H), 2.44 (s, 3 H), 4.54 - 4.63 (m, 1 H), 6.46 (d, J=8.6 Hz, 2 H), 7.21 - 7.29 (m, 1 H), 7.30 - 7.38 (m, 1 H), 7.63 (d, J=7.9 Hz, 1 H), 7.69 (d, J=7.7 Hz, 1 H), 7.75 (d, J=8.6 Hz, 2 H).

(4) 3-{[(4-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

Using 4-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}benzoic acid (300 mg) synthesized above and in the same manner as in Example A1(4), the title object compound (275 mg, 77%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.01 - 1.34 (m, 5 H), 1.53 - 1.85 (m, 5 H), 2.03 - 2.14 (m, 1 H), 2.44 (s, 3 H), 2.53 (t, J=5.6

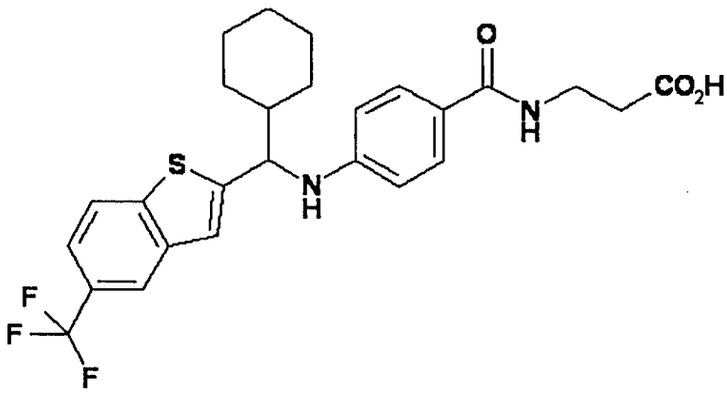
Hz, 2 H), 3.50 - 3.61 (m, 2 H), 4.54 (d, J=7.7 Hz, 1 H), 6.48 (d, J=8.8 Hz, 2 H), 6.58 (t, J=5.9 Hz, 1 H), 7.20 - 7.27 (m, 1 H), 7.29 - 7.37 (m, 1 H), 7.46 (d, J=8.8 Hz, 2 H), 7.62 (d, J=7.5 Hz, 1 H), 7.67 (d, J=7.5 Hz, 1 H).

[0799]

Example A11

3-({[4-({cyclohexyl[5-(trifluoromethyl)-1-benzothiophen-2-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0800]




[0801]

(1) 3-methyl-5-(trifluoromethyl)-1-benzothiophene-2-carbaldehyde

To a solution (40 mL) of methyl 3-methyl-5-(trifluoromethyl)-1-benzothiophene-2-carboxylate (2.00 g) in tetrahydrofuran was added lithium aluminum hydride (292 mg) at 0°C, and the mixture was stirred for 1 hr. Water (300 µL) was added to quench the reaction, 1N aqueous sodium hydroxide solution (300 µL) was added, and the mixture was stirred at room temperature for 3 hr. The resulting insoluble material was filtered off, and the filtrate was concentrated under reduced pressure to give a white solid. To a solution of the obtained solid in tetrahydrofuran (40 mL) was added active manganese dioxide (9.00 g), and the mixture was stirred overnight at room temperature. Manganese dioxide was filtered off, and the filtrate was concentrated under reduced pressure to give the title object compound (1.15 g, 65%) as a brown

solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 7.69 - 7.75 (m, 1 H), 8.00 - 8.06 (m, 1 H), 8.11 (s, 1 H), 8.21 - 8.25 (m, 1 H), 10.14 (s, 1 H).

(2) cyclohexyl[3-methyl-5-(trifluoromethyl)-1-benzothiophen-2-yl]methanol

Using 3-methyl-5-(trifluoromethyl)-1-benzothiophene-2-carbaldehyde (1.15 g) synthesized above and in the same manner as in Example A1(1), the title object compound (860 mg, 55%) was obtained as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 - 1.35 (m, 5 H), 1.50 - 1.59 (m, 1 H), 1.62 - 1.85 (m, 4 H), 1.95 - 2.06 (m, 1 H), 2.12 - 2.18 (m, 1 H), 4.75 (d, J=7.2 Hz, 1 H), 7.22 (s, 1 H), 7.48 - 7.53 (m, 1 H), 7.87 - 7.92 (m, 1 H), 7.97 (s, 1 H).

(3) 2-[chloro(cyclohexyl)methyl]-3-methyl-5-(trifluoromethyl)-1-benzothiophene

To a solution of cyclohexyl[3-methyl-5-(trifluoromethyl)-1-benzothiophen-2-yl]methanol (860 mg) synthesized above in toluene (20 mL) was added thionyl chloride (239 μL), and the mixture was stirred at 100°C for 1 hr. The reaction mixture was poured into ice-cooled saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (806 mg, 89%) as a pale-brown oil

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.99 - 1.37 (m, 5 H), 1.58 - 2.01 (m, 5 H), 2.13 - 2.23 (m, 1 H), 4.97 (d, J=7.8 Hz, 1 H), 7.29 (s, 1 H), 7.51 - 7.56 (m, 1 H), 7.86 - 7.91 (m, 1 H), 7.96 - 7.99 (m, 1 H).

(4) 4-({cyclohexyl[3-methyl-5-(trifluoromethyl)-1-benzothiophen-2-yl]methyl}amino)benzoic acid

Using 2-[chloro(cyclohexyl)methyl]-3-methyl-5-(trifluoromethyl)-1-benzothiophene (806 mg) synthesized above and in the same manner as in Example A1(3), the title object compound (68.7 mg, 7%) was obtained as a pale-yellow oil.

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$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.07 - 1.37 (m, 5 H), 1.62 - 1.89 (m, 5 H), 1.90 - 2.00 (m, 1 H), 4.58 (d, J=6.3 Hz, 1 H), 6.59 (d, J=8.7 Hz, 2 H), 7.25 (s, 1 H), 7.45 - 7.50 (m, 1 H), 7.82 (d, J=8.4 Hz, 1 H), 7.84 (d, J=8.7 Hz, 2 H), 7.93 - 7.96 (m, 1 H).

(5) 3-({[4-({cyclohexyl[5-(trifluoromethyl)-1-benzothiophen-2-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

Using 4-({cyclohexyl[3-methyl-5-(trifluoromethyl)-1-benzothiophen-2-yl]methyl}amino)benzoic acid (68.7 mg) synthesized above and in the same manner as in Example A1(4), the title object compound (57.8 mg, 73%) was obtained as a white solid.

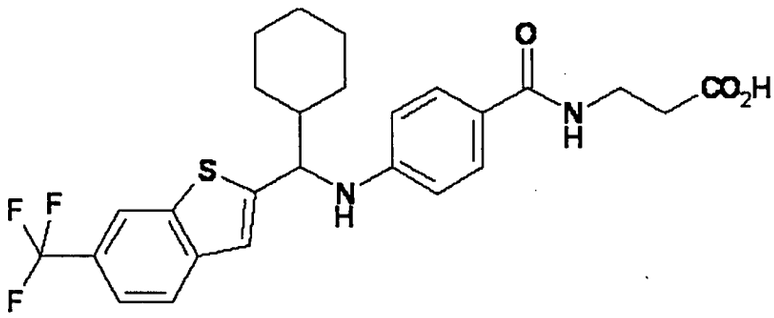
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.36 (m, 5 H), 1.59 - 1.87 (m, 5 H), 1.88 - 1.99 (m, 1 H), 2.58 (t, J=5.3 Hz, 2 H), 3.54 - 3.66 (m, 2 H), 4.51 (d, J=6.4 Hz, 1 H), 6.56 (d, J=8.3 Hz, 2 H), 6.63 (t, J=5.7 Hz, 1 H), 7.22 (s, 1 H), 7.43 - 7.49 (m, 1 H), 7.51 (d, J=8.3 Hz, 2 H), 7.80 (d, J=8.7 Hz, 1 H), 7.93 (s, 1 H).

[0802]

Example A12

3-({[4-({cyclohexyl[6-(trifluoromethyl)-1-benzothiophen-2-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0803]




[0804]

(1) 3-methyl-6-(trifluoromethyl)-1-benzothiophene-2-carbaldehyde

Using methyl 3-methyl-6-(trifluoromethyl)-1-benzothiophene-2-carboxylate (2.07 g) and in the same manner

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as in Example A11(1), the title object compound (1.38 g, 75%) was obtained as a brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 7.63 - 7.69 (m, 1 H), 8.06 (d, J=8.4 Hz, 1 H), 8.08 (s, 1 H), 8.18 - 8.22 (m, 1 H), 10.15 (s, 1 H).

(2) cyclohexyl[3-methyl-6-(trifluoromethyl)-1-benzothiophen-2-yl]methanol

Using 3-methyl-6-(trifluoromethyl)-1-benzothiophene-2-carbaldehyde (1.38 g) synthesized above and in the same manner as in Example A1(1), the title object compound (668 mg, 35%) was obtained as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.99 - 1.35 (m, 5 H), 1.50 - 1.60 (m, 1 H), 1.62 - 1.84 (m, 4 H), 1.94 - 2.04 (m, 1 H), 2.15 - 2.20 (m, 1 H), 4.76 (dd, J=6.9, 3.6 Hz, 1 H), 7.21 (s, 1 H), 7.52 - 7.58 (m, 1 H), 7.79 (d, J=8.1 Hz, 1 H), 8.06 - 8.10 (m, 1 H).

(3) 2-[chloro(cyclohexyl)methyl]-3-methyl-6-(trifluoromethyl)-1-benzothiophene

Using cyclohexyl[3-methyl-6-(trifluoromethyl)-1-benzothiophen-2-yl]methanol (668 mg) synthesized above and in the same manner as in Example A11(3), the title object compound (659 mg, 93%) was obtained as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 1.37 (m, 5 H), 1.58 - 1.86 (m, 4 H), 1.88 - 2.01 (m, 1 H), 2.12 - 2.22 (m, 1 H), 4.97 (d, J=7.8 Hz, 1 H), 7.28 (s, 1 H), 7.53 - 7.58 (m, 1 H), 7.80 (d, J=8.4 Hz, 1 H), 8.05 - 8.08 (m, 1 H).

(4) 4-({cyclohexyl[3-methyl-6-(trifluoromethyl)-1-benzothiophen-2-yl]methyl}amino)benzoic acid

Using 2-[chloro(cyclohexyl)methyl]-3-methyl-6-(trifluoromethyl)-1-benzothiophene (659 mg) synthesized above and in the same manner as in Example A1(3), the title object compound (82.5 mg, 10%) was obtained as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.37 (m, 5 H), 1.62 - 1.88 (m, 5 H), 1.90 - 1.99 (m, 1 H), 4.58 (d, J=6.3 Hz, 1 H), 6.59 (d, J=8.7 Hz, 2 H), 7.23 (s, 1 H), 7.50 - 7.55 (m, 1 H), 7.76

(d, J=8.4 Hz, 1 H), 7.84 (d, J=8.7 Hz, 2 H), 7.99 - 8.02 (m, 1 H).

(5) 3-({[4-({cyclohexyl[6-(trifluoromethyl)-1-benzothiophen-2-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

Using 4-({cyclohexyl[3-methyl-6-(trifluoromethyl)-1-benzothiophen-2-yl]methyl}amino)benzoic acid (82.5 mg) synthesized above and in the same manner as in Example A1(4), the title object compound (54.0 mg, 56%) was obtained as a white solid.

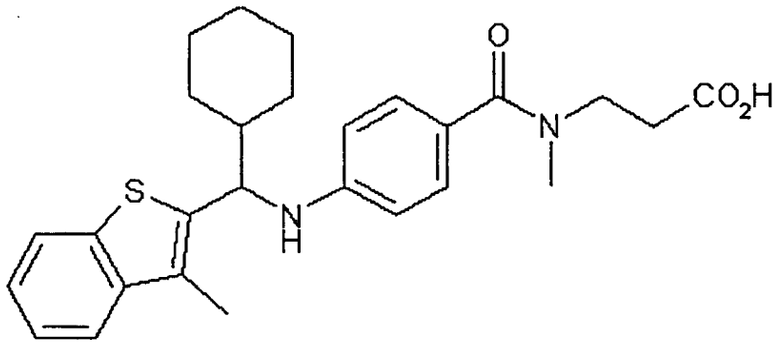
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 - 1.35 (m, 5 H), 1.58 - 1.87 (m, 5 H), 1.88 - 1.99 (m, 1 H), 2.53 - 2.63 (m, 2 H), 3.54 - 3.66 (m, 2 H), 4.52 (d, J=6.1 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.58 - 6.66 (m, 1 H), 7.20 (s, 1 H), 7.46 - 7.55 (m, 3 H), 7.73 (d, J=8.3 Hz, 1 H), 7.98 (s, 1 H).

[0805]

Example A13

3-{[(4-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0806]




[0807]

Using 4-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}benzoic acid (300 mg) synthesized in Example A10(3) and ethyl 3-(methylamino)propanoate (124 mg) and in the same manner as in Example A1(4), the title object compound (269 mg, 73%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.34 (m, 5 H), 1.53 - 1.87 (m, 5 H), 2.05 - 2.16 (m, 1 H), 2.45 (s, 3 H), 2.59 (t, J=6.4

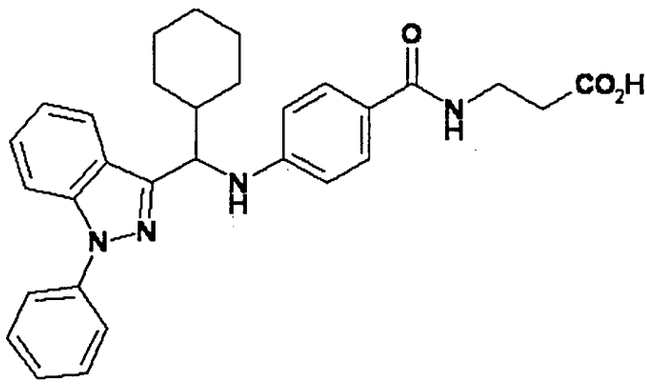
Hz, 2 H), 2.97 (s, 3 H), 3.65 (t, J=6.4 Hz, 2 H), 4.53 (d, J=7.5 Hz, 1 H), 6.50 (d, J=8.7 Hz, 2 H), 7.18 (d, J=8.7 Hz, 2 H), 7.22 - 7.29 (m, 1 H), 7.30 - 7.38 (m, 1 H), 7.63 (d, J=7.5 Hz, 1 H), 7.70 (d, J=7.7 Hz, 1 H).

[0808]

Example A14

3-{[(4-{[cyclohexyl(1-phenyl-1H-indazol-3-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0809]




[0810]

(1) methyl 1-phenyl-1H-indazole-3-carboxylate

To a mixture of methyl 1H-indazole-3-carboxylate (3.44 g), phenylboronic acid (4.76 g), pyridine (2.84 mL) and N,N-dimethylformamide (70 mL) was added copper (II) acetate (5.32 g), and the mixture was stirred at 30°C overnight. The insoluble material was filtered off, saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated sodium hydrogen carbonate and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (1.58 g, 32%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 4.07 (s, 3 H), 7.35 - 7.60 (m, 5 H), 7.70 - 7.77 (m, 3 H), 8.30 - 8.35 (m, 1 H).

(2) 1-phenyl-1H-indazole-3-carbaldehyde

To a solution (40 mL) of methyl 1-phenyl-1H-indazole-3-carboxylate (2.25 g) synthesized above in tetrahydrofuran was added dropwise 1.5M diisobutylaluminum hydride toluene solution (26.7 mL) at 0°C, and the mixture was stirred for 1 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with 1N hydrochloric acid and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a colorless oil. To a solution of the obtained oil in tetrahydrofuran (40 mL) was added active manganese dioxide (8.00 g), and the mixture was stirred at 50°C for 5 hr. Active manganese dioxide (1.00 g) was additionally added, and the mixture was stirred at 50°C for 1 hr. Manganese dioxide was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=3:17, volume ratio) to give the title object compound (926 mg, 47%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 7.39 - 7.47 (m, 1 H), 7.47 - 7.55 (m, 2 H), 7.57 - 7.64 (m, 2 H), 7.72 - 7.80 (m, 3 H), 8.37 - 8.42 (m, 1 H), 10.34 (s, 1 H).

(3) cyclohexyl(1-phenyl-1H-indazol-3-yl)methanol

Using 1-phenyl-1H-indazole-3-carbaldehyde (926 mg) synthesized above and in the same manner as in Example A1(1), the title object compound (716 mg, 56%) was obtained as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.11 - 1.31 (m, 5 H), 1.51 - 1.84 (m, 4 H), 1.94 - 2.08 (m, 2 H), 2.52 (d, J=4.5 Hz, 1 H), 4.93 - 5.00 (m, 1 H), 7.18 - 7.25 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.39 - 7.45 (m, 1 H), 7.49 - 7.56 (m, 2 H), 7.68 - 7.74 (m, 3 H), 7.87 - 7.92 (m, 1 H).

(4) 3-[chloro(cyclohexyl)methyl]-1-phenyl-1H-indazole

To a mixture of cyclohexyl(1-phenyl-1H-indazol-3-yl)methanol (716 mg) synthesized above, pyridine (284 μL) and

toluene (20 mL) was added thionyl chloride (256 μL), and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (767 mg, quantitative) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.99 - 1.38 (m, 5 H), 1.46 - 1.55 (m, 1 H), 1.60 - 1.72 (m, 2 H), 1.80 - 1.90 (m, 1 H), 2.24 - 2.44 (m, 2 H), 5.15 (d, J=9.0 Hz, 1 H), 7.21 - 7.27 (m, 1 H), 7.32 - 7.39 (m, 1 H), 7.40 - 7.46 (m, 1 H), 7.49 - 7.56 (m, 2 H), 7.67 - 7.74 (m, 3 H), 7.96 - 8.00 (m, 1 H).

(5) 3-{[(4-{[cyclohexyl(1-phenyl-1H-indazol-3-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

Using 3-[chloro(cyclohexyl)methyl]-1-phenyl-1H-indazole (370 mg) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (269 mg) synthesized in Example 1(2) and in the same manner as in Example A7(3), the title object compound (79.1 mg, 14%) was obtained as a pale-yellow solid.

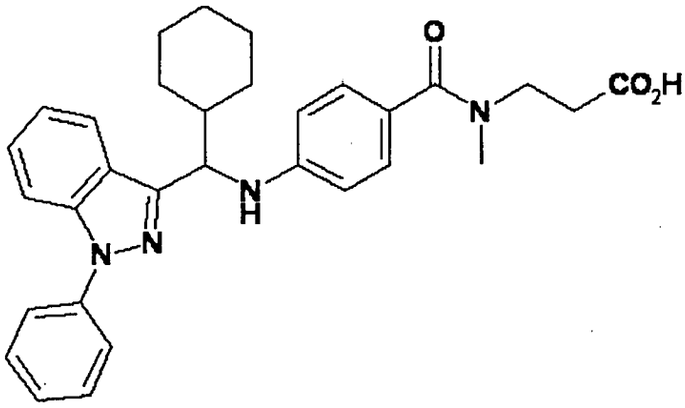
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.01 - 1.36 (m, 5 H), 1.54 - 1.84 (m, 4 H), 1.98 - 2.13 (m, 2 H), 2.52 - 2.64 (m, 2 H), 3.53 - 3.66 (m, 2 H), 4.81 (d, J=6.8 Hz, 1 H), 6.52 - 6.71 (m, 3 H), 7.16 (t, J=7.6 Hz, 1 H), 7.29 - 7.42 (m, 2 H), 7.45 - 7.56 (m, 4 H), 7.62 - 7.71 (m, 3 H), 7.81 (d, J=8.3 Hz, 1 H).

[0811]

Example A15

3-{[(4-{[cyclohexyl(1-phenyl-1H-indazol-3-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0812]



[0813]

Using 3-[chloro(cyclohexyl)methyl]-1-phenyl-1H-indazole (397 mg) synthesized in Example A14(4) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (305 mg) synthesized in Example 2(2) and in the same manner as in Example A7(3), the title object compound (76.9 mg, 12%) was obtained as a pale-yellow solid.

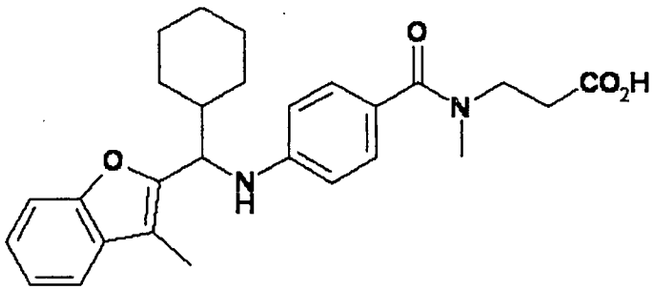
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 - 1.35 (m, 5 H), 1.54 - 1.84 (m, 4 H), 1.98 - 2.13 (m, 2 H), 2.56 - 2.67 (m, 2 H), 2.99 (s, 3 H), 3.67 (t, J=6.1 Hz, 2 H), 4.80 (d, J=6.4 Hz, 1 H), 6.66 (d, J=8.7 Hz, 2 H), 7.13 - 7.18 (m, 1 H), 7.21 (d, J=8.7 Hz, 2 H), 7.30 - 7.42 (m, 2 H), 7.52 (t, J=7.8 Hz, 2 H), 7.64 - 7.72 (m, 2 H), 7.82 (d, J=8.3 Hz, 1 H).

[0814]

Example A16

3-{[(4-{[cyclohexyl(3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0815]



[0816]

337

(1) 3-methyl-1-benzofuran-2-carbaldehyde

To a solution (40 mL) of ethyl 3-methyl-1-benzofuran-2-carboxylate (2.00 g) in tetrahydrofuran was added dropwise 1.5M diisobutylaluminum hydride toluene solution (19.6 mL) at 0°C, and the mixture was stirred for 2 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a white solid. To a solution (40 mL) of the obtained solid in dichloromethane was added Dess-Martin periodinane (4.96 g) at 0°C, and the mixture was stirred at room temperature overnight. Saturated sodium sulfite aqueous solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:9, volume ratio) to give the title object compound (753 mg, 48%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.63 (s, 3 H), 7.30 - 7.37 (m, 1 H), 7.48 - 7.58 (m, 2 H), 7.67 - 7.71 (m, 1 H), 10.03 (s, 1 H).

(2) cyclohexyl(3-methyl-1-benzofuran-2-yl)methanol

Using 3-methyl-1-benzofuran-2-carbaldehyde (753 mg) synthesized above and in the same manner as in Example A1(1), the title object compound (843 mg, 73%) was obtained as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 - 1.03 (m, 1 H), 1.03 - 1.34 (m, 4 H), 1.34 - 1.44 (m, 1 H), 1.60 - 1.71 (m, 2 H), 1.75 - 1.99 (m, 3 H), 2.10 - 2.20 (m, 1 H), 2.23 (s, 3 H), 4.49 - 4.56 (m, 1 H), 7.18 - 7.29 (m, 2 H), 7.39 - 7.49 (m, 2 H).

(3) 2-[chloro(cyclohexyl)methyl]-3-methyl-1-benzofuran

To a mixture of cyclohexyl(3-methyl-1-benzofuran-2-yl)methanol (843 mg) synthesized above and toluene (20 mL) was added thionyl chloride (256 μL), and the mixture was stirred at

room temperature for 2.5 hr and at 50°C for 1.5 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (862 mg, 95%) as a yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 - 0.98 (m, 1 H), 1.00 - 1.37 (m, 4 H), 1.42 - 1.53 (m, 1 H), 1.57 - 1.77 (m, 2 H), 1.77 - 1.88 (m, 1 H), 2.12 - 2.28 (m, 4 H), 2.08 - 2.38 (m, 1 H), 4.82 (d, J=9.6 Hz, 1 H), 7.14 - 7.33 (m, 2 H), 7.43 - 7.50 (m, 2 H).

(4) 3-{[(4-{[cyclohexyl(3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

Using 2-[chloro(cyclohexyl)methyl]-3-methyl-1-benzofuran (429 mg) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (408 mg) synthesized in Example 2(2) and in the same manner as in Example A7(3), the title object compound (247 mg, 34%) was obtained as a white solid.

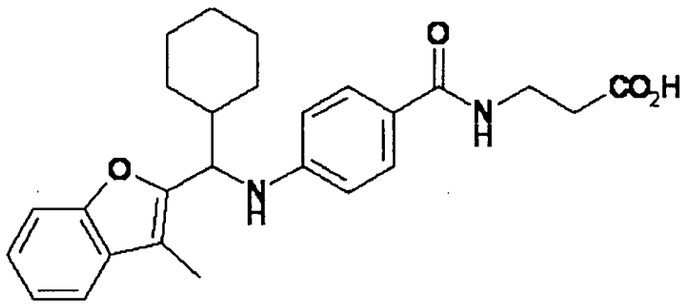
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.37 (m, 5 H), 1.47 - 1.58 (m, 1 H), 1.60 - 1.73 (m, 2 H), 1.73 - 1.83 (m, 1 H), 1.84 - 1.98 (m, 1 H), 2.03 - 2.15 (m, 1 H), 2.25 (s, 3 H), 2.59 - 2.69 (m, 2 H), 3.01 (s, 2 H), 3.68 (t, J=6.5 Hz, 2 H), 4.38 (d, J=7.9 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 7.16 - 7.27 (m, 4 H), 7.35 - 7.40 (m, 1 H), 7.41 - 7.45 (m, 1 H).

[0817]

Example A17

3-{[(4-{[cyclohexyl(3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0818]



[0819]

Using 2-[chloro(cyclohexyl)methyl]-3-methyl-1-benzofuran (433 mg) synthesized in Example A16(3) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (390 mg) synthesized in Example 1(2) and in the same manner as in Example A7(3), the title object compound (268 mg, 37%) was obtained as a white solid.

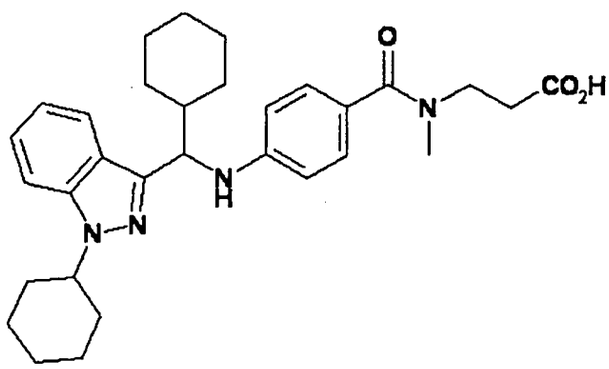
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.37 (m, 5 H), 1.46 - 1.59 (m, 1 H), 1.59 - 1.74 (m, 2 H), 1.74 - 1.84 (m, 1 H), 1.84 - 1.99 (m, 1 H), 2.02 - 2.13 (m, 1 H), 2.25 (s, 3 H), 2.55 - 2.66 (m, 2 H), 3.57 - 3.68 (m, 2 H), 4.40 (d, J=8.1 Hz, 1 H), 6.51 - 6.65 (m, 3 H), 7.14 - 7.25 (m, 2 H), 7.34 - 7.39 (m, 1 H), 7.39 - 7.45 (m, 1 H), 7.52 (d, J=8.9 Hz, 2 H).

[0820]

Example A18

3-{[(4-{[cyclohexyl(1-cyclohexyl-1H-indazol-3-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0821]



[0822]

(1) methyl 1-cyclohexyl-1H-indazole-3-carboxylate

340

To a mixture of methyl 1H-indazole-3-carboxylate (5.00 g), cyclohexanol (9.00 mL), triphenylphosphine (14.9 g) and tetrahydrofuran (100 mL) was added 40% diethyl azodicarboxylate toluene solution (25.6 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, diethyl ether was added to the residue, and the mixture was stirred at 0°C. The precipitate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:9, volume ratio) to give the title object compound (6.84 g, 93%) as a pale-red oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.25 - 1.43 (m, 1 H), 1.45 - 1.62 (m, 2 H), 1.72 - 1.82 (m, 1 H), 1.90 - 2.00 (m, 2 H), 2.01 - 2.16 (m, 4 H), 4.03 (s, 3 H), 5.50 - 5.62 (m, 1 H), 7.24 - 7.37 (m, 2 H), 7.78 - 7.83 (m, 1 H), 7.99 - 8.04 (m, 1 H).

(2) 1-cyclohexyl-1H-indazole-3-carbaldehyde

Using methyl 1-cyclohexyl-1H-indazole-3-carboxylate (3.08 g) synthesized above and in the same manner as in Example A14(2), the title object compound (1.98 g, 73%) was obtained as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 - 1.43 (m, 1 H), 1.45 - 1.63 (m, 2 H), 1.74 - 1.84 (m, 1 H), 1.92 - 2.02 (m, 2 H), 2.06 - 2.18 (m, 4 H), 5.24 - 5.36 (m, 1 H), 7.33 - 7.43 (m, 2 H), 7.83 - 7.90 (m, 1 H), 7.98 - 8.05 (m, 1 H), 10.32 (s, 1 H).

(3) cyclohexyl(1-cyclohexyl-1H-indazol-3-yl)methanol

Using 1-cyclohexyl-1H-indazole-3-carbaldehyde (980 mg) synthesized above and in the same manner as in Example A1(1), the title object compound (984 mg, 73%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.82 - 1.00 (m, 1 H), 1.05 - 2.07 (m, 17 H), 2.07 - 2.33 (m, 4 H), 4.48 - 4.62 (m, 1 H), 4.93 (dd, J=8.9, 3.6 Hz, 1 H), 6.99 - 7.07 (m, 1 H), 7.20 - 7.28 (m, 1 H), 7.65 - 7.73 (m, 2 H).

(4) 3-[chloro(cyclohexyl)methyl]-1-cyclohexyl-1H-indazole

341

Using cyclohexyl(1-cyclohexyl-1H-indazol-3-yl)methanol (934 mg) synthesized above and in the same manner as in Example A14(4), the title object compound (1.05 g, quantitative) was obtained as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.75 - 0.89 (m, 1 H), 1.06 - 2.08 (m, 16 H), 2.09 - 2.38 (m, 3 H), 2.45 - 2.56 (m, 1 H), 4.41 - 4.54 (m, 1 H), 5.09 (d, J=10.5 Hz, 1 H), 7.04 - 7.11 (m, 1 H), 7.21 - 7.29 (m, 1 H), 7.66 - 7.72 (m, 2 H).

(5) 3-{[(4-{[cyclohexyl(1-cyclohexyl-1H-indazol-3-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

Using 3-[chloro(cyclohexyl)methyl]-1-cyclohexyl-1H-indazole (400 mg) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (303 mg) synthesized in Example 2(2) and in the same manner as in Example A7(3), the title object compound (451 mg, 72%) was obtained as a white solid.

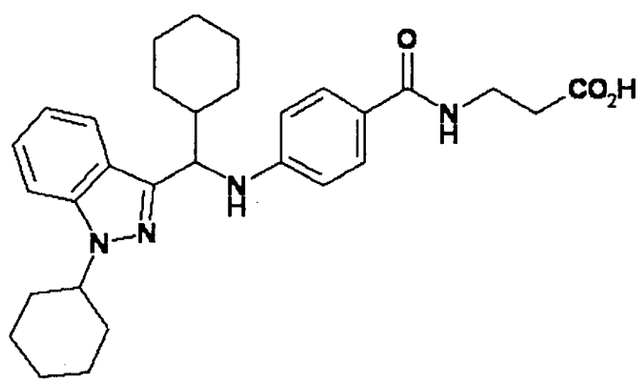
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.50 (m, 9 H), 1.61 - 2.04 (m, 9 H), 2.06 - 2.29 (m, 3 H), 2.57 - 2.69 (m, 2 H), 2.99 (s, 3 H), 3.67 (t, J=6.2 Hz, 2 H), 4.43 - 4.57 (m, 1 H), 4.72 (d, J=8.3 Hz, 1 H), 6.47 (d, J=8.7 Hz, 2 H), 6.99 - 7.06 (m, 1 H), 7.17 (d, J=8.7 Hz, 2 H), 7.20 - 7.29 (m, 1 H), 7.65 - 7.73 (m, 4 H).

[0823]

Example A19

3-{[(4-{[cyclohexyl(1-cyclohexyl-1H-indazol-3-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0824]



342

[0825]

Using 3-[chloro(cyclohexyl)methyl]-1-cyclohexyl-1H-indazole (400 mg) synthesized in Example A18(4) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (286 mg) synthesized in Example 1(2) and in the same manner as in Example A7(3), the title object compound (441 mg, 72%) was obtained as a white solid.

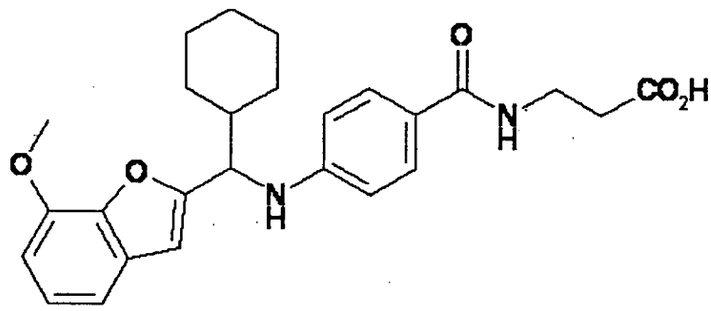
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.48 (m, 9 H), 1.61 - 2.04 (m, 9 H), 2.03 - 2.29 (m, 3 H), 2.61 (t, J=5.7 Hz, 2 H), 3.54 - 3.69 (m, 2 H), 4.43 - 4.55 (m, 1 H), 4.74 (d, J=8.3 Hz, 1 H), 6.46 (d, J=8.7 Hz, 2 H), 6.67 (t, J=5.8 Hz, 1 H), 6.97 - 7.06 (m, 1 H), 7.18 - 7.29 (m, 1 H), 7.46 (d, J=8.7 Hz, 2 H), 7.68 (d, J=9.4 Hz, 2 H).

[0826]

Example A20

3-{[(4-{[cyclohexyl(7-methoxy-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0827]



[0828]

(1) 7-methoxy-1-benzofuran-2-carbaldehyde

Using ethyl 7-methoxy-1-benzofuran-2-carboxylate (2.00 g) and in the same manner as in Example A14(2), the title object compound (950 mg, 59%) was obtained as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 4.04 (s, 3 H), 6.96 - 7.00 (m, 1 H), 7.22 - 7.34 (m, 2 H), 7.54 (s, 1 H), 9.90 (s, 1 H).

(2) cyclohexyl(7-methoxy-1-benzofuran-2-yl)methanol

Using 7-methoxy-1-benzofuran-2-carbaldehyde (950 mg)

synthesized above and in the same manner as in Example A1(1), the title object compound (790 mg, 56%) was obtained as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.34 (m, 5 H), 1.49 - 1.60 (m, 1 H), 1.60 - 1.83 (m, 3 H), 1.84 - 2.02 (m, 3 H), 4.00 (s, 3 H), 4.53 - 4.59 (m, 1 H), 6.60 (s, 1 H), 6.74 - 6.81 (m, 1 H), 7.09 - 7.17 (m, 2 H).

(3) 2-[chloro(cyclohexyl)methyl]-7-methoxy-1-benzofuran

Using cyclohexyl(7-methoxy-1-benzofuran-2-yl)methanol (790 mg) synthesized above and in the same manner as in Example A1(2), the title object compound (823 mg, 97%) was obtained as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.37 (m, 5 H), 1.55 - 1.84 (m, 4 H), 2.06 - 2.25 (m, 2 H), 4.01 (s, 3 H), 4.81 (d, J=7.8 Hz, 1 H), 6.67 (s, 1 H), 6.75 - 6.83 (m, 1 H), 7.10 - 7.18 (m, 2 H).

(4) 3-{[(4-{[cyclohexyl(7-methoxy-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

Using 2-[chloro(cyclohexyl)methyl]-7-methoxy-1-benzofuran (422 mg) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (357 mg) synthesized in Example 1(2) and in the same manner as in Example A7(3), the title object compound (64.3 mg, 9%) was obtained as a pale-yellow solid.

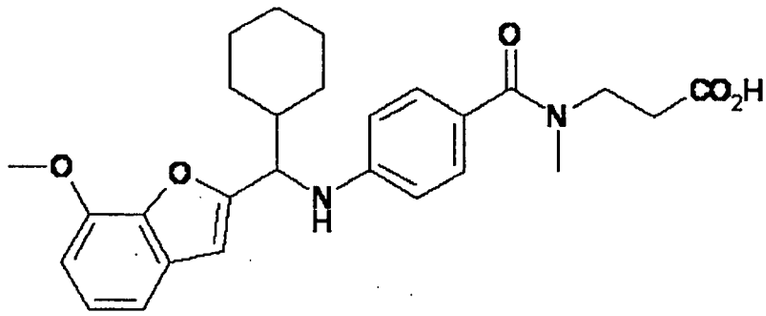
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.34 (m, 5 H), 1.54 - 1.82 (m, 4 H), 1.87 - 2.07 (m, 2 H), 2.64 (t, J=5.6 Hz, 2 H), 3.59 - 3.69 (m, 2 H), 4.00 (s, 3 H), 4.43 (d, J=6.4 Hz, 1 H), 6.50 (s, 1 H), 6.53 - 6.61 (m, 3 H), 6.75 (dd, J=7.5, 1.3 Hz, 1 H), 7.02 - 7.13 (m, 2 H), 7.53 (d, J=8.7 Hz, 2 H).

[0829]

Example A21

3-{[(4-{[cyclohexyl(7-methoxy-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0830]



[0831]

Using 2-[chloro(cyclohexyl)methyl]-7-methoxy-1-benzofuran (401 mg) synthesized in Example A20(3) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (360 mg) synthesized in Example 2(2) and in the same manner as in Example A7(3), the title object compound (48.7 mg, 7%) was obtained as a white solid.

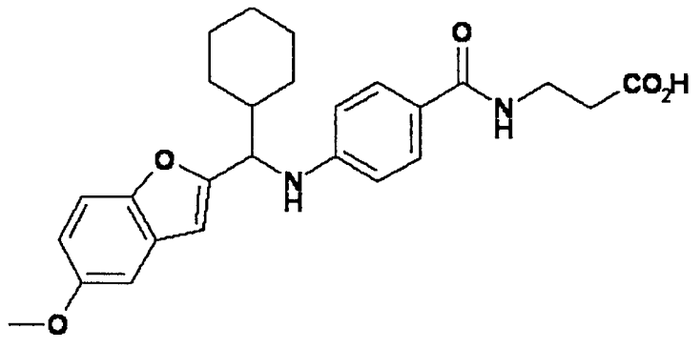
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 - 1.34 (m, 5 H), 1.54 - 1.82 (m, 4 H), 1.88 - 2.08 (m, 2 H), 2.68 (t, J=6.4 Hz, 2 H), 3.04 (s, 3 H), 3.71 (t, J=6.4 Hz, 2 H), 4.01 (s, 3 H), 4.42 (d, J=6.6 Hz, 1 H), 6.51 (s, 1 H), 6.57 (d, J=8.7 Hz, 2 H), 6.76 (dd, J=7.3, 1.5 Hz, 1 H), 7.04 - 7.15 (m, 2 H), 7.24 (d, J=8.7 Hz, 2 H).

[0832]

Example A22

3-{[(4-{[cyclohexyl(5-methoxy-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0833]



[0834]

(1) 5-methoxy-1-benzofuran-2-carbaldehyde

345

Using ethyl 5-methoxy-1-benzofuran-2-carboxylate (2.00 g) and in the same manner as in Example A14(2), the title object compound (914 mg, 57%) was obtained as a brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.86 (s, 3 H), 7.10 - 7.16 (m, 2 H), 7.46 - 7.52 (m, 2 H), 9.82 (s, 1 H).

(2) cyclohexyl(5-methoxy-1-benzofuran-2-yl)methanol

Using 5-methoxy-1-benzofuran-2-carbaldehyde (914 mg) synthesized above and in the same manner as in Example A1(1), the title object compound (702 mg, 52%) was obtained as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 - 1.35 (m, 5 H), 1.47 - 1.58 (m, 1 H), 1.60 - 2.02 (m, 6 H), 3.83 (s, 3 H), 4.47 - 4.53 (m, 1 H), 6.54 (s, 1 H), 6.85 (dd, J=8.7, 2.7 Hz, 1 H), 6.99 (d, J=2.7 Hz, 1 H), 7.33 (d, J=8.7 Hz, 1 H).

(3) 2-[chloro(cyclohexyl)methyl]-5-methoxy-1-benzofuran

Using cyclohexyl(5-methoxy-1-benzofuran-2-yl)methanol (702 mg) synthesized above and in the same manner as in Example A1(2), the title object compound (722 mg, 96%) was obtained as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 - 1.38 (m, 5 H), 1.51 - 1.86 (m, 4 H), 2.06 - 2.21 (m, 2 H), 3.83 (s, 3 H), 4.75 (d, J=8.1 Hz, 1 H), 6.59 - 6.61 (m, 1 H), 6.88 (dd, J=8.9, 2.4 Hz, 1 H), 6.97 (d, J=2.4 Hz, 1 H), 7.33 - 7.38 (m, 1 H).

(4) 3-{[(4-{[cyclohexyl(5-methoxy-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of 2-[chloro(cyclohexyl)methyl]-5-methoxy-1-benzofuran (360 mg) synthesized above, ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (305 mg) synthesized in Example 1(2), sodium iodide (291 mg) and N,N-dimethylacetamide (10 mL) was added sodium carbonate (206 mg), and the mixture was stirred at 80°C overnight. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column

chromatography (ethyl acetate:hexane=11:9, volume ratio) to give a yellow oil. To a mixture of the obtained oil, tetrahydrofuran (2.5 mL) and ethanol (2.5 mL) was added 1N aqueous sodium hydroxide solution (1 mL), and the mixture was stirred at room temperature for 4 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in water (5 mL), and 1N hydrochloric acid (1 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (96.0 mg, 17%) as a yellow solid.

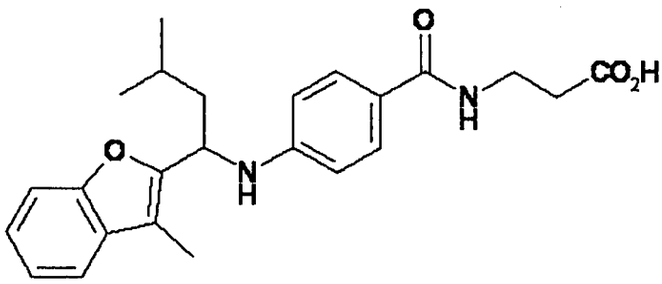
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.35 (m, 5 H), 1.54 - 1.84 (m, 4 H), 1.85 - 2.01 (m, 2 H), 2.60 - 2.69 (m, 2 H), 3.59 - 3.70 (m, 2 H), 3.80 (s, 3 H), 4.38 (d, J=6.4 Hz, 1 H), 6.44 (s, 1 H), 6.53 - 6.62 (m, 3 H), 6.82 (dd, J=9.1, 2.7 Hz, 1 H), 6.92 (d, J=2.7 Hz, 1 H), 7.30 (d, J=9.1 Hz, 1 H), 7.54 (d, J=8.7 Hz, 2 H).

[0835]

Example A23

3-{[(4-{[3-methyl-1-(3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl]amino}propanoic acid

[0836]




[0837]

(1) N-methoxy-N,3-dimethyl-1-benzofuran-2-carboxamide

To a mixture of 3-methyl-1-benzofuran-2-carboxylic acid (15.0 g), N,O-dimethylhydroxyamine hydrochloride (9.95 g), 1-hydroxybenzotriazole·monohydrate (15.6 g), triethylamine (14.2 mL) and N,N-dimethylformamide (150 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (19.6 g), and

the mixture was stirred overnight at room temperature. In addition, N,O-dimethylhydroxyamine hydrochloride (4.16 g), 1-hydroxybenzotriazole·monohydrate (6.52 g), triethylamine (5.94 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (8.17 g) were added, and the mixture was stirred at room temperature for 4 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=3:7, volume ratio) to give the title object compound (16.2 g, 87%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.51 (s, 3 H), 3.39 (s, 3 H), 3.87 (s, 3 H), 7.25 - 7.32 (m, 1 H), 7.37 - 7.50 (m, 2 H), 7.58 - 7.63 (m, 1 H).

(2) 3-methyl-1-(3-methyl-1-benzofuran-2-yl)butan-1-one

To a solution (20 mL) of N-methoxy-N,3-dimethyl-1-benzofuran-2-carboxamide (1.00 g) synthesized above in tetrahydrofuran was added dropwise a 1.0M solution (6.84 mL) of isobutylmagnesium bromide in tetrahydrofuran at 0°C, and the mixture was stirred for 1 hr. In addition, 1.0M isobutylmagnesium bromide tetrahydrofuran solution (6.84 mL) was added, and the mixture was stirred at 0°C for 1 hr then at room temperature for 2 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:9, volume ratio) to give the title object compound (873 mg, 89%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 (d, J=6.9 Hz, 6 H), 2.26 - 2.41 (m, 1 H), 2.61 (s, 3 H), 2.87 (d, J=6.9 Hz, 2 H), 7.26 -

348

7.33 (m, 1 H), 7.42 - 7.53 (m, 2 H), 7.62 - 7.67 (m, 1 H).

(3) methyl 4-{[3-methyl-1-(3-methyl-1-benzofuran-2-yl)butyl]amino}benzoate

To a mixture of 3-methyl-1-(3-methyl-1-benzofuran-2-yl)butan-1-one (200 mg) synthesized above, methyl 4-aminobenzoate (140 mg), triethylamine (1.03 mL) and dichloromethane (5 mL) was added titanium (IV) chloride (122 μL) at 0°C, and the mixture was stirred at room temperature overnight. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown solid. To a mixture of the obtained solid, acetic acid (1 mL), methanol (5 mL) and tetrahydrofuran (5 mL) was added sodium cyanoborohydride (175 mg) by small portions, and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (254 mg, 78%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 (d, J=6.6 Hz, 3 H), 1.01 (d, J=6.6 Hz, 3 H), 1.49 - 1.64 (m, 1 H), 1.79 - 1.96 (m, 2 H), 2.29 (s, 3 H), 3.81 (s, 3 H), 4.48 (d, J=7.8 Hz, 1 H), 4.70 - 4.80 (m, 1 H), 6.58 (d, J=8.9 Hz, 2 H), 7.16 - 7.26 (m, 2 H), 7.34 - 7.39 (m, 1 H), 7.41 - 7.45 (m, 1 H), 7.80 (d, J=8.9 Hz, 2 H).

(4) 4-{[3-methyl-1-(3-methyl-1-benzofuran-2-yl)butyl]amino}benzoic acid

To a mixture of methyl 4-{[3-methyl-1-(3-methyl-1-benzofuran-2-yl)butyl]amino}benzoate (1.38 g) synthesized above, tetrahydrofuran (20 mL) and ethanol (20 mL) was added

1N aqueous sodium hydroxide solution (20 mL), and the mixture was stirred with heating under reflux overnight. In addition, 1N aqueous sodium hydroxide solution (20 mL) was added, and the mixture was stirred with heating under reflux for 3 hr. The reaction mixture was concentrated under reduced pressure, 1N hydrochloric acid (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title object compound (1.06 g, 80%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 (d, J=6.6 Hz, 3 H), 1.01 (d, J=6.6 Hz, 3 H), 1.49 - 1.64 (m, 1 H), 1.79 - 1.97 (m, 2 H), 2.30 (s, 3 H), 4.77 (t, J=7.5 Hz, 1 H), 6.59 (d, J=9.0 Hz, 2 H), 7.16 - 7.28 (m, 2 H), 7.35 - 7.40 (m, 1 H), 7.42 - 7.47 (m, 1 H), 7.86 (d, J=9.0 Hz, 2 H).

(5) 3-{[(4-{[3-methyl-1-(3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl]amino}propanoic acid

Using 4-{[3-methyl-1-(3-methyl-1-benzofuran-2-yl)butyl]amino}benzoic acid (300 mg) synthesized above and in the same manner as in Example A1(4), the title object compound (289 mg, 80%) was obtained as a white solid.

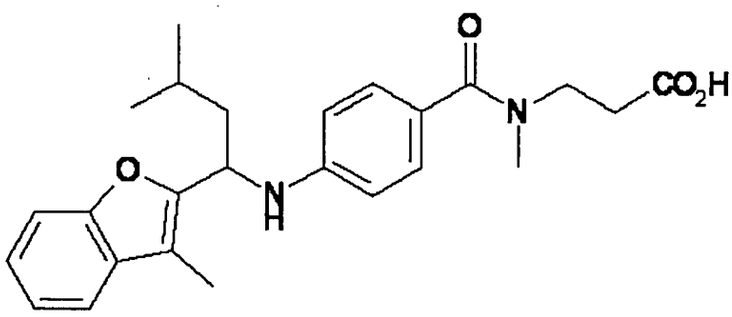
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.6 Hz, 3 H), 1.00 (d, J=6.6 Hz, 3 H), 1.48 - 1.64 (m, 1 H), 1.78 - 1.94 (m, 2 H), 2.28 (s, 3 H), 2.64 (t, J=5.5 Hz, 2 H), 3.60 - 3.69 (m, 2 H), 4.73 (t, J=7.5 Hz, 1 H), 6.54 - 6.65 (m, 3 H), 7.15 - 7.26 (m, 2 H), 7.34 - 7.39 (m, 1 H), 7.40 - 7.45 (m, 1 H), 7.54 (d, J=8.7 Hz, 2 H).

[0838]

Example A24

3-{methyl[(4-{[3-methyl-1-(3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl]amino}propanoic acid

[0839]



[0840]

Using 4-{[3-methyl-1-(3-methyl-1-benzofuran-2-yl)butyl]amino}benzoic acid (300 mg) synthesized in Example A23(4) and ethyl 3-(methylamino)propanoate (140 mg) and in the same manner as in Example A1(4), the title object compound (221 mg, 59%) was obtained as a white solid.

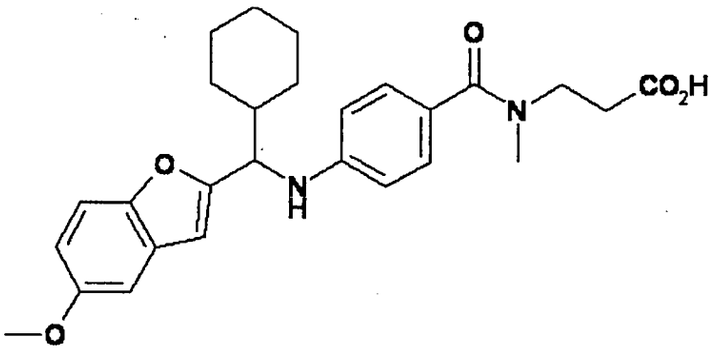
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.6 Hz, 3 H), 1.00 (d, J=6.6 Hz, 3 H), 1.48 - 1.64 (m, 1 H), 1.81 - 1.92 (m, 2 H), 2.29 (s, 3 H), 2.61 - 2.71 (m, 2 H), 3.03 (s, 3 H), 3.70 (t, J=6.4 Hz, 2 H), 4.71 (t, J=7.5 Hz, 1 H), 6.58 (d, J=8.5 Hz, 2 H), 7.16 - 7.29 (m, 6 H), 7.35 - 7.40 (m, 1 H), 7.41 - 7.46 (m, 1 H).

[0841]

Example A25

3-{[(4-{[cyclohexyl(5-methoxy-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0842]



[0843]

Using 2-[chloro(cyclohexyl)methyl]-5-methoxy-1-benzofuran (361 mg) synthesized in Example A22(3) and ethyl 3-{[(4-

aminophenyl)carbonyl](methyl)amino}propanoate (325 mg) synthesized in Example 2(2) and in the same manner as in Example A22(4), the title object compound (87.0 mg, 14%) was obtained as a white solid.

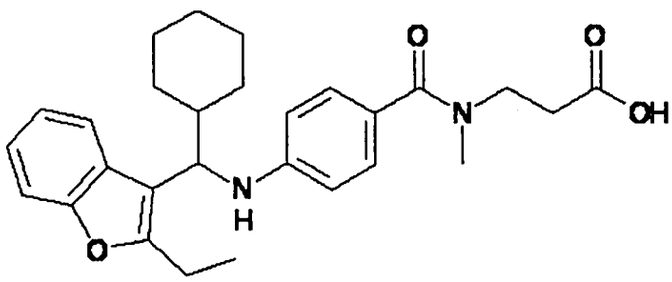
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.36 (m, 5 H), 1.55 - 1.84 (m, 4 H), 1.86 - 2.01 (m, 2 H), 2.61 - 2.74 (m, 2 H), 3.04 (s, 3 H), 3.71 (t, J=6.2 Hz, 2 H), 3.81 (s, 3 H), 4.36 (d, J=6.1 Hz, 1 H), 6.45 (s, 1 H), 6.57 (d, J=8.7 Hz, 2 H), 6.83 (dd, J=8.9, 2.5 Hz, 1 H), 6.94 (d, J=2.5 Hz, 1 H), 7.21 - 7.29 (m, 2 H), 7.31 (d, J=8.9 Hz, 1 H).

[0844]

Example A26

3-{[(4-{[cyclohexyl(2-ethyl-1-benzofuran-3-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0845]




[0846]

(1) cyclohexyl(2-ethyl-1-benzofuran-3-yl)methanol

Using 2-ethyl-1-benzofuran-3-carbaldehyde (1.20 g) and in the same manner as in Example A1(1), the title object compound (1.76 g, 99%) was obtained as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.79 - 0.94 (m, 1 H), 1.01 - 1.19 (m, 3 H), 1.20 - 1.34 (m, 4 H), 1.37 - 1.46 (m, 1 H), 1.57 - 1.70 (m, 2 H), 1.77 - 2.02 (m, 3 H), 2.17 - 2.27 (m, 1 H), 2.70 - 2.85 (m, 2 H), 4.54 (dd, J=8.7, 2.7 Hz, 1 H), 7.14 - 7.24 (m, 2 H), 7.37 - 7.41 (m, 1 H), 7.60 - 7.65 (m, 1 H).

(2) 3-[chloro(cyclohexyl)methyl]-2-ethyl-1-benzofuran

Using cyclohexyl(2-ethyl-1-benzofuran-3-yl)methanol (763 mg) synthesized above and in the same manner as in Example

A1(2), the title object compound (765 mg, 94%) was obtained as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.75 - 0.89 (m, 1 H), 1.00 - 1.39 (m, 7 H), 1.43 - 1.53 (m, 1 H), 1.58 - 1.69 (m, 2 H), 1.78 - 1.89 (m, 1 H), 2.12 - 2.26 (m, 1 H), 2.35 - 2.46 (m, 1 H), 2.70 - 2.85 (m, 2 H), 4.78 (d, J=9.9 Hz, 1 H), 7.14 - 7.28 (m, 2 H), 7.37 - 7.42 (m, 1 H), 7.67 - 7.72 (m, 1 H).

(3) 3-{[(4-{[cyclohexyl(2-ethyl-1-benzofuran-3-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

Using 3-[chloro(cyclohexyl)methyl]-2-ethyl-1-benzofuran (300 mg) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (270 mg) synthesized in Example 2(2) and in the same manner as in Example A22(4), the title object compound (287 mg, 57%) was obtained as a white solid.

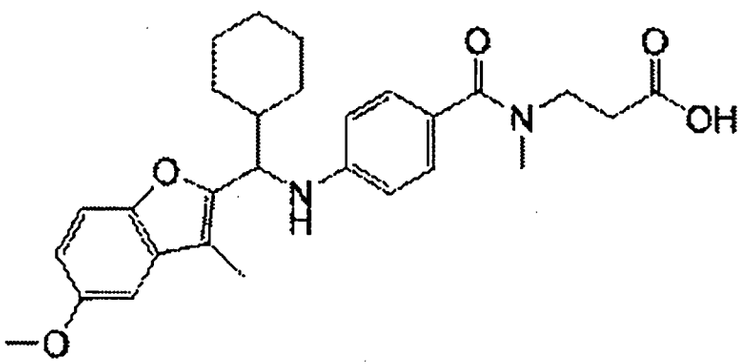
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.87 - 1.23 (m, 5 H), 1.28 (t, J=7.5 Hz, 3 H), 1.55 - 1.75 (m, 3 H), 1.75 - 1.98 (m, 2 H), 2.04 - 2.15 (m, 1 H), 2.61 - 2.71 (m, 2 H), 2.75 - 2.90 (m, 2 H), 3.02 (s, 3 H), 3.69 (t, J=6.4 Hz, 2 H), 4.30 (d, J=7.9 Hz, 1 H), 6.49 (d, J=8.7 Hz, 2 H), 7.12 - 7.24 (m, 4 H), 7.35 - 7.41 (m, 1 H), 7.53 - 7.59 (m, 1 H).

[0847]

Example A27

3-{[(4-{[cyclohexyl(5-methoxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0848]



[0849]

(1) methyl 5-methoxy-3-methyl-1-benzofuran-2-carboxylate

To a mixture of 1-(2-hydroxy-5-methoxyphenyl)ethanone (5.00 g), methyl bromoacetate (3.13 mL) and N,N-dimethylformamide (50 mL) was added potassium carbonate (12.5 g), and the mixture was stirred overnight at room temperature. Water was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a brown oil. To a solution (50 mL) of the obtained oil in methanol was added sodium methoxide (1.63 g), and the mixture was stirred with heating under reflux for 3 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (1.25 g, 19%) as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.57 (s, 3 H), 3.87 (s, 3 H), 3.97 (s, 3 H), 6.99 (d, J=2.6 Hz, 1 H), 7.06 (dd, J=9.0, 2.6 Hz, 1 H), 7.42 (d, J=9.0 Hz, 1 H).

(2) 5-methoxy-3-methyl-1-benzofuran-2-carbaldehyde

To a solution (100 mL) of methyl 5-methoxy-3-methyl-1-benzofuran-2-carboxylate (5.00 g) in tetrahydrofuran was added lithium aluminum hydride (862 mg) at 0°C, and the mixture was stirred for 1.5 hr. Water (860 μL) was added to quench the reaction, 1N aqueous sodium hydroxide solution (860 μL) was added, and the mixture was stirred at room temperature for 1 hr. The resulting insoluble material was filtered off, and the filtrate was concentrated under reduced pressure to give a pale-yellow solid. To a solution of the obtained solid in tetrahydrofuran (80 mL) was added active manganese dioxide (21.2 g), and the mixture was stirred at 50°C overnight. Manganese dioxide was filtered off, and the filtrate was concentrated under reduced pressure to give the title object

compound (3.41 g, 79%) as a brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.60 (s, 3 H), 3.88 (s, 3 H), 7.03 (d, J=2.5 Hz, 1 H), 7.14 (dd, J=9.0, 2.5 Hz, 1 H), 7.44 (d, J=9.0 Hz, 1 H), 10.00 (s, 1 H).

(3) cyclohexyl(5-methoxy-3-methyl-1-benzofuran-2-yl)methanol

Using 5-methoxy-3-methyl-1-benzofuran-2-carbaldehyde (1.50 g) synthesized above as in Example A1(1), the title object compound (1.54 g, 71%) was obtained as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 - 0.99 (m, 1 H), 1.00 - 1.33 (m, 4 H), 1.33 - 1.44 (m, 1 H), 1.60 - 1.70 (m, 2 H), 1.74 - 1.99 (m, 3 H), 2.09 - 2.22 (m, 4 H), 3.85 (s, 3 H), 4.50 (dd, J=8.6, 6.5 Hz, 1 H), 6.86 (dd, J=8.7, 2.6 Hz, 1 H), 6.91 (d, J=2.6 Hz, 1 H), 7.30 (d, J=8.7 Hz, 1 H).

(4) 2-[chloro(cyclohexyl)methyl]-5-methoxy-3-methyl-1-benzofuran

Using cyclohexyl(5-methoxy-3-methyl-1-benzofuran-2-yl)methanol (754 mg) synthesized above and in the same manner as in Example A1(2), the title object compound (795 mg, 99%) was obtained as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.83 - 0.97 (m, 1 H), 1.00 - 1.40 (m, 4 H), 1.42 - 1.52 (m, 1 H), 1.60 - 1.70 (m, 2 H), 1.77 - 1.87 (m, 1 H), 2.10 - 2.38 (m, 5 H), 3.85 (s, 3 H), 4.80 (d, J=9.6 Hz, 1 H), 6.86 - 6.91 (m, 2 H), 7.31 - 7.36 (m, 1 H).

(5) 3-{[(4-{[cyclohexyl(5-methoxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

Using 2-[chloro(cyclohexyl)methyl]-5-methoxy-3-methyl-1-benzofuran (395 mg) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (338 mg) synthesized in Example 2(2) and in the same manner as in Example A22(4), the title object compound (305 mg, 47%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.37 (m, 5 H), 1.47 - 1.57 (m, 1 H), 1.60 - 1.96 (m, 4 H), 2.03 - 2.13 (m, 1 H), 2.23 (s, 3 H), 2.65 (t, J=6.4 Hz, 2 H), 3.02 (s, 3 H), 3.69 (t, J=6.4 Hz, 2 H), 3.83 (s, 3 H), 4.36 (d, J=8.0 Hz, 1 H), 6.55 (d,

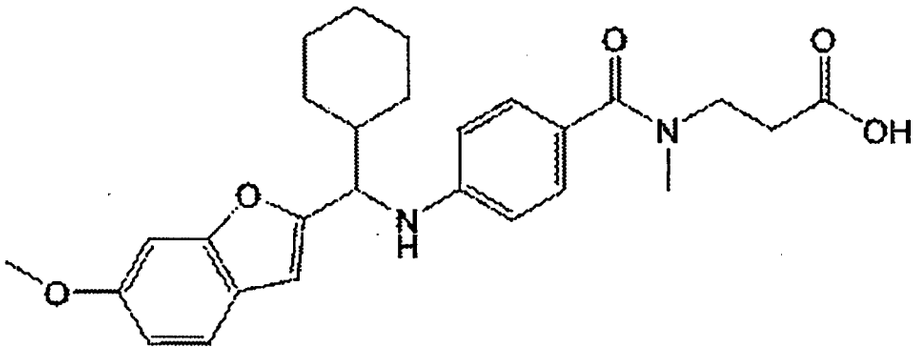
J=8.7 Hz, 2 H), 6.82 (dd, J=8.9, 2.4 Hz, 1 H), 6.88 (d, J=2.4 Hz, 1 H), 7.19 - 7.29 (m, 3 H).

[0850]

Example A28

3-{[(4-{[cyclohexyl(6-methoxy-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0851]



[0852]

(1) 6-methoxy-1-benzofuran-2-carbonitrile

To a mixture of 2-hydroxy-4-methoxybenzaldehyde (10.0 g), bromoacetonitrile (5.04 mL) and acetone (100 mL) was added potassium carbonate (18.1 g), and the mixture was stirred at room temperature for 3 hr. The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure to give a pale-brown solid. To a solution (100 mL) of the obtained solid in N,N-dimethylformamide was added 1,8-diazabicyclo[5.4.0]undec-7-ene (9.83 mL), and the mixture was stirred at 140°C for 1.5 hr. The reaction mixture was concentrated under reduced pressure, 1N hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. Ethyl acetate was added to the residue, the insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=3:17, volume ratio) to give the title object compound (5.32 g, 47%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.88 (s, 3 H), 6.96 - 7.04 (m, 2 H), 7.39 (d, J=0.9 Hz, 1 H), 7.52 (d, J=8.5 Hz, 1 H).

(2)cyclohexyl(6-methoxy-1-benzofuran-2-yl)methanone

To a solution (20 mL) of 6-methoxy-1-benzofuran-2-carbonitrile (1.00 g) synthesized above in tetrahydrofuran was added 1.0M cyclohexylmagnesium bromide tetrahydrofuran solution (11.5 mL), and the mixture was stirred at 50°C overnight, and stirred with heating under reflux for 1 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:9, volume ratio) to give the title object compound (584 mg, 39%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.20 - 1.64 (m, 5 H), 1.69 - 1.79 (m, 1 H), 1.81 - 1.98 (m, 4 H), 3.09 - 3.21 (m, 1 H), 3.87 (s, 3 H), 6.93 (dd, J=8.4, 2.1 Hz, 1 H), 7.03 - 7.06 (m, 1 H), 7.44 - 7.46 (m, 1 H), 7.54 (d, J=8.4 Hz, 1 H).

(3) methyl 4-{[cyclohexyl(6-methoxy-1-benzofuran-2-yl)methyl]amino}benzoate

Using cyclohexyl(6-methoxy-1-benzofuran-2-yl)methanone (584 mg) synthesized above and in the same manner as in Example A23(3), the title object compound (682 mg, 77%) was obtained as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 - 1.36 (m, 5 H), 1.56 - 1.84 (m, 4 H), 1.86 - 2.00 (m, 2 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 4.35 - 4.57 (m, 2 H), 6.44 (s, 1 H), 6.58 (d, J=8.9 Hz, 1 H), 6.81 (dd, J=8.6, 2.3 Hz, 1 H), 6.97 (d, J=2.3 Hz, 1 H), 7.31 (d, J=8.6 Hz, 1 H), 7.80 (d, J=8.9 Hz, 2 H).

(4) 4-{[cyclohexyl(6-methoxy-1-benzofuran-2-yl)methyl]amino}benzoic acid

Using methyl 4-{[cyclohexyl(6-methoxy-1-benzofuran-2-yl)methyl]amino}benzoate (682 mg) synthesized above and in the same manner as in Example A23(4), the title object compound

(633 mg, 96%) was obtained as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.37 (m, 5 H), 1.56 - 1.86 (m, 4 H), 1.86 - 2.01 (m, 2 H), 3.83 (s, 3 H), 4.36 - 4.46 (m, 1 H), 4.48 - 4.65 (m, 1 H), 6.45 (s, 1 H), 6.60 (d, J=8.9 Hz, 2 H), 6.82 (dd, J=8.6, 2.3 Hz, 1 H), 6.98 (d, J=2.3 Hz, 1 H), 7.33 (d, J=8.6 Hz, 1 H), 7.86 (d, J=8.9 Hz, 2 H).

(5) 3-{[(4-{[cyclohexyl(6-methoxy-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

Using 4-{[cyclohexyl(6-methoxy-1-benzofuran-2-yl)methyl]amino}benzoic acid (300 mg) synthesized above and ethyl 3-(methylamino)propanoate (125 mg) and in the same manner as in Example A1(4), the title object compound (201 mg, 55%) was obtained as a white solid.

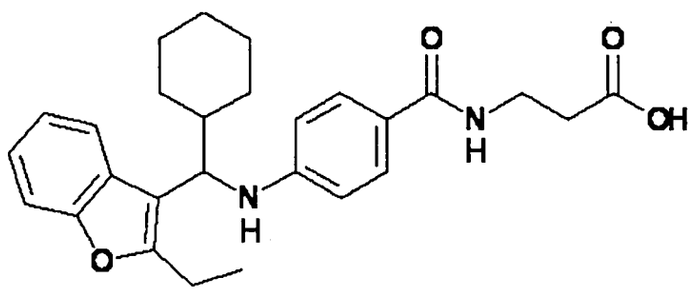
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 - 1.36 (m, 5 H), 1.55 - 1.84 (m, 4 H), 1.85 - 2.00 (m, 2 H), 2.67 (t, J=6.5 Hz, 2 H), 3.03 (s, 3 H), 3.70 (t, J=6.5 Hz, 2 H), 3.83 (s, 3 H), 4.35 (d, J=6.6 Hz, 1 H), 6.44 (s, 1 H), 6.57 (d, J=8.7 Hz, 2 H), 6.82 (dd, J=8.5, 2.2 Hz, 1 H), 6.98 (d, J=2.2 Hz, 1 H), 7.22 - 7.28 (m, 2 H), 7.32 (d, J=8.5 Hz, 1 H).

[0853]

Example A29

3-{[(4-{[cyclohexyl(2-ethyl-1-benzofuran-3-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0854]




[0855]

Using 3-[chloro(cyclohexyl)methyl]-2-ethyl-1-benzofuran (300 mg) synthesized in Example A26(2) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (255 mg) synthesized in

Example 1(2) and in the same manner as in Example A22(4), the title object compound (374 mg, 77%) was obtained as a pale-brown solid.

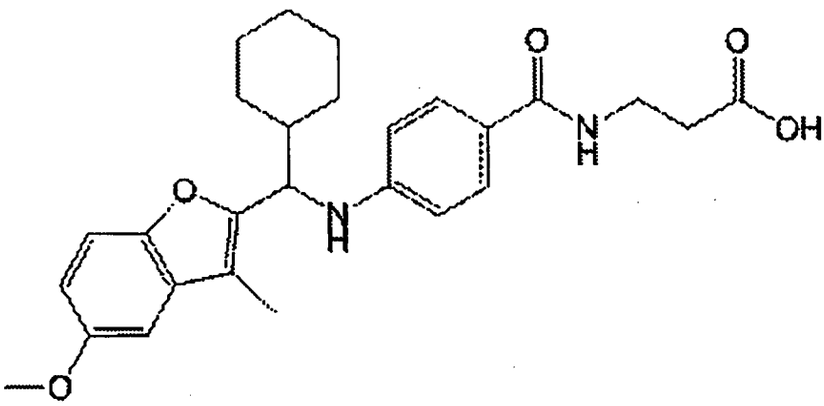
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.23 (m, 5 H), 1.27 (t, J=7.5 Hz, 3 H), 1.55 - 1.74 (m, 3 H), 1.76 - 1.97 (m, 2 H), 2.04 - 2.15 (m, 1 H), 2.56 - 2.66 (m, 2 H), 2.71 - 2.92 (m, 2 H), 3.56 - 3.66 (m, 2 H), 4.31 (d, J=7.9 Hz, 1 H), 6.48 (d, J=8.7 Hz, 2 H), 6.52 - 6.62 (m, 1 H), 7.11 - 7.22 (m, 2 H), 7.34 - 7.40 (m, 1 H), 7.47 (d, J=8.7 Hz, 2 H), 7.52 - 7.57 (m, 1 H).

[0856]

Example A30

3-{[(4-{[cyclohexyl(5-methoxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0857]



[0858]

Using 2-[chloro(cyclohexyl)methyl]-5-methoxy-3-methyl-1-benzofuran (395 mg) synthesized in Example A27(4) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (319 mg) synthesized in Example 1(2) and in the same manner as in Example A22(4), the title object compound (413 mg, 66%) was obtained as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.36 (m, 5 H), 1.46 - 1.58 (m, 1 H), 1.60 - 1.97 (m, 4 H), 2.01 - 2.13 (m, 1 H), 2.22 (s, 3 H), 2.61 (t, J=5.9 Hz, 2 H), 3.57 - 3.67 (m, 2 H), 3.82 (s, 3 H), 4.37 (d, J=8.0 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.61

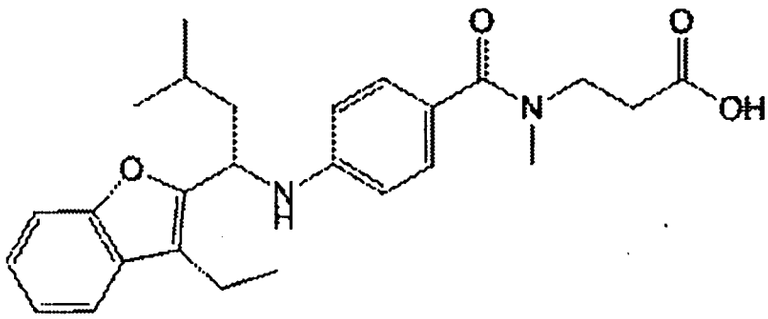
(t, J=6.1 Hz, 1 H), 6.81 (dd, J=9.1, 2.7 Hz, 1 H), 6.87 (d, J=2.3 Hz, 1 H), 7.21 - 7.28 (m, 1 H), 7.52 (d, J=8.7 Hz, 2 H).

[0859]

Example A31

3-{[(4-{[1-(3-ethyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0860]



[0861]

(1) methyl 3-ethyl-1-benzofuran-2-carboxylate

To a mixture of 1-(2-hydroxyphenyl)propan-1-one (10.0 g), methyl bromoacetate (5.11 mL) and acetone (100 mL) was added potassium carbonate (18.4 g), and the mixture was stirred overnight at room temperature. The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give a colorless oil. To a solution (150 mL) of the obtained oil in N,N-dimethylformamide was added 1,8-diazabicyclo[5.4.0]undec-7-ene (8.12 mL), and the mixture was stirred at 120°C for 2 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. Ethyl acetate was added to the residue, the insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:9, volume ratio) to give the title object compound (7.14 g, 52%)

as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 (t, J=7.5 Hz, 4 H), 3.12 (q, J=7.5 Hz, 2 H), 3.99 (s, 3 H), 7.27 - 7.34 (m, 1 H), 7.41 - 7.49 (m, 1 H), 7.53 - 7.58 (m, 1 H), 7.65 - 7.70 (m, 1 H).

(2) 3-ethyl-1-benzofuran-2-carbaldehyde

Using methyl 3-ethyl-1-benzofuran-2-carboxylate (3.00 g) synthesized above and in the same manner as in Example A27(2), the title object compound (2.27 g, 90%) was obtained as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.40 (t, J=7.6 Hz, 3 H), 3.12 (q, J=7.6 Hz, 2 H), 7.30 - 7.37 (m, 1 H), 7.48 - 7.60 (m, 2 H), 7.71 - 7.76 (m, 1 H), 10.04 (s, 1 H).

(3) 1-(3-ethyl-1-benzofuran-2-yl)-3-methylbutan-1-ol

To a solution (50 mL) of 3-ethyl-1-benzofuran-2-carbaldehyde (2.27 g) synthesized above in tetrahydrofuran was added dropwise 1.0M isobutylmagnesium bromide tetrahydrofuran solution (19.5 mL) at 0°C, and the mixture was stirred for 1 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=3:17, volume ratio) to give the title object compound (1.55 g, 51%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 (d, J=6.6 Hz, 3 H), 0.96 (d, J=6.6 Hz, 3 H), 1.28 (t, J=7.5 Hz, 3 H), 1.56 - 1.73 (m, 1 H), 1.74 - 1.86 (m, 2 H), 1.88 - 1.99 (m, 1 H), 2.74 (q, J=7.5 Hz, 2 H), 4.91 - 4.99 (m, 1 H), 7.18 - 7.31 (m, 2 H), 7.41 - 7.47 (m, 1 H), 7.50 - 7.56 (m, 1 H).

(4) 2-(1-chloro-3-methylbutyl)-3-ethyl-1-benzofuran

Using 1-(3-ethyl-1-benzofuran-2-yl)-3-methylbutan-1-ol (1.00 g) synthesized above and in the same manner as in Example A1(2), the title object compound (1.03 g, 96%) was obtained as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 0.97 (m, 6 H), 1.29 (t,

J=7.5 Hz, 3 H), 1.60 - 1.75 (m, 1 H), 2.14 - 2.21 (m, 2 H), 2.73 (q, J=7.5 Hz, 2 H), 5.22 (t, J=8.0 Hz, 1 H), 7.19 - 7.33 (m, 2 H), 7.41 - 7.48 (m, 1 H), 7.51 - 7.55 (m, 1 H).

(5) 3-{[(4-{[1-(3-ethyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

Using 2-(1-chloro-3-methylbutyl)-3-ethyl-1-benzofuran (300 mg) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (300 mg) synthesized in Example 2(2) and in the same manner as in Example A22(4), the title object compound (97.4 mg, 19%) was obtained as a yellow solid.

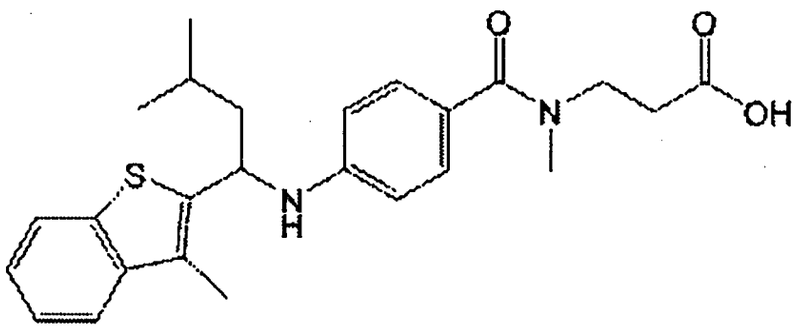
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 (d, J=6.6 Hz, 3 H), 1.00 (d, J=6.4 Hz, 3 H), 1.27 (t, J=7.6 Hz, 3 H), 1.51 - 1.69 (m, 1 H), 1.82 - 1.89 (m, 2 H), 2.60 - 2.70 (m, 2 H), 2.77 (q, J=7.6 Hz, 2 H), 3.02 (s, 3 H), 3.69 (t, J=6.4 Hz, 2 H), 4.72 (t, J=7.5 Hz, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 7.15 - 7.28 (m, 4 H), 7.36 - 7.42 (m, 1 H), 7.47 - 7.52 (m, 1 H).

[0862]

Example A32

3-{methyl[(4-{[3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}phenyl)carbonyl]amino}propanoic acid

[0863]




[0864]

(1) 3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butan-1-one

To a mixture of 3-methyl-1-benzothiophene (5.00 g), isovaleryl chloride (4.52 mL) and nitromethane (50 mL) was added aluminum (III) chloride (8.98 g) at 0°C, and the mixture

was stirred at 0°C for 30 min then at room temperature for 4 hr. The reaction mixture was poured into ice-cooled water, and the mixture was extracted with ethyl acetate. The extract was washed with 1N hydrochloric acid and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:19, volume ratio) to give the title object compound (7.72 g, 99%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 (d, J=6.8 Hz, 6 H), 2.28 - 2.43 (m, 1 H), 2.77 (s, 3 H), 2.80 (d, J=7.0 Hz, 2 H), 7.39 - 7.53 (m, 2 H), 7.81 - 7.90 (m, 2 H).

(2) methyl 4-{[3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}benzoate

Using 3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butan-1-one (1.00 g) synthesized above and in the same manner as in Example A23(3), the title object compound (923 mg, 58%) was obtained as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 (d, J=6.0 Hz, 3 H), 1.02 (d, J=6.0 Hz, 3 H), 1.68 - 1.81 (m, 2 H), 1.81 - 1.95 (m, 1 H), 2.47 (s, 3 H), 3.80 (s, 3 H), 4.40 - 4.47 (m, 1 H), 4.86 - 4.95 (m, 1 H), 6.54 (d, J=8.1 Hz, 2 H), 7.23 - 7.30 (m, 1 H), 7.32 - 7.39 (m, 1 H), 7.62 - 7.67 (m, 2 H), 7.69 - 7.74 (m, 1 H), 7.79 (d, J=8.1 Hz, 2 H).

(3) 4-{[3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}benzoic acid

Using methyl 4-{[3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}benzoate (923 mg) synthesized above and in the same manner as in Example A23(4), the title object compound (817 mg, 92%) was obtained as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 (d, J=6.2 Hz, 3 H), 1.02 (d, J=6.2 Hz, 3 H), 1.67 - 1.96 (m, 3 H), 2.47 (s, 3 H), 4.88 - 4.96 (m, 1 H), 6.55 (d, J=8.9 Hz, 2 H), 7.23 - 7.30 (m, 1 H), 7.32 - 7.39 (m, 1 H), 7.62 - 7.68 (m, 1 H), 7.69 - 7.74 (m, 1 H), 7.84 (d, J=8.9 Hz, 2 H).

(4) 3-{methyl[(4-{[3-methyl-1-(3-methyl-1-benzothiophen-2-

yl)butyl]amino}phenyl)carbonyl]amino}propanoic acid

Using 4-{[3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}benzoic acid (300 mg) synthesized above and ethyl 3-(methylamino)propanoate (134 mg) and in the same manner as in Example A1(4), the title object compound (218 mg, 59%) was obtained as a white solid.

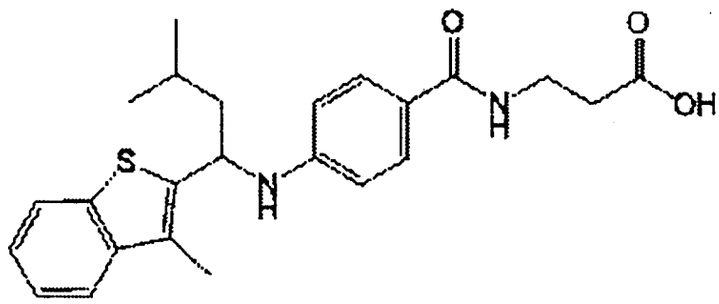
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 (d, J=6.2 Hz, 3 H), 1.02 (d, J=6.2 Hz, 3 H), 1.66 - 1.94 (m, 3 H), 2.46 (s, 3 H), 2.62 - 2.72 (m, 2 H), 3.02 (s, 3 H), 3.70 (t, J=6.4 Hz, 2 H), 4.82 - 4.89 (m, 1 H), 6.54 (d, J=8.7 Hz, 2 H), 7.20 - 7.31 (m, 3 H), 7.32 - 7.39 (m, 1 H), 7.65 (d, J=7.9 Hz, 1 H), 7.72 (d, J=7.3 Hz, 1 H).

[0865]

Example A33

3-{[(4-{[3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}phenyl)carbonyl]amino}propanoic acid

[0866]




[0867]

Using 4-{[3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}benzoic acid (300 mg) synthesized in Example A32(3) and in the same manner as in Example A1(4), the title object compound (316 mg, 88%) was obtained as a white solid.

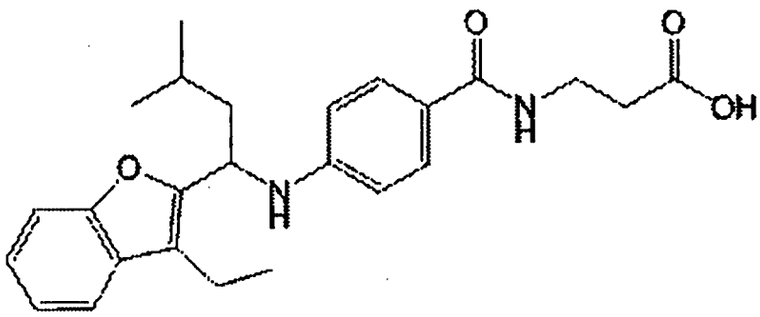
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 (d, J=6.0 Hz, 3 H), 1.01 (d, J=6.2 Hz, 3 H), 1.66 - 1.94 (m, 3 H), 2.46 (s, 3 H), 2.61 (t, J=5.7 Hz, 2 H), 3.57 - 3.67 (m, 2 H), 4.83 - 4.91 (m, 1 H), 6.50 - 6.62 (m, 3 H), 7.22 - 7.29 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.51 (d, J=8.7 Hz, 2 H), 7.64 (d, J=7.5 Hz, 1 H), 7.70 (d, J=7.9 Hz, 1 H).

[0868]

Example A34

3-{[(4-{[1-(3-ethyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl]amino}propanoic acid

[0869]



[0870]

Using 2-(1-chloro-3-methylbutyl)-3-ethyl-1-benzofuran (300 mg) synthesized in Example A31(4) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (283 mg) synthesized in Example 1(2) and in the same manner as in Example A22(4), the title object compound (162 mg, 32%) was obtained as a pale-brown solid.

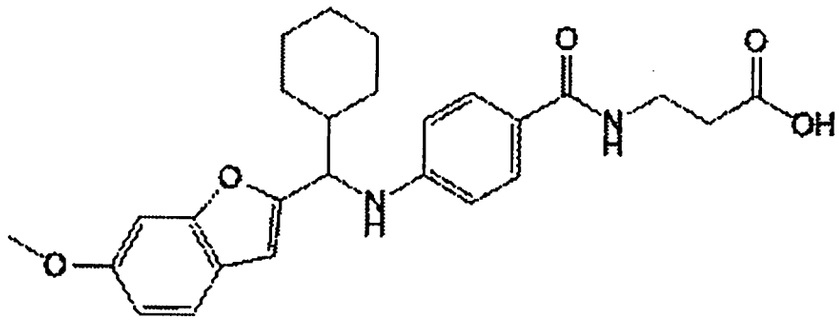
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.6 Hz, 3 H), 1.00 (d, J=6.6 Hz, 3 H), 1.27 (t, J=7.5 Hz, 3 H), 1.51 - 1.68 (m, 1 H), 1.81 - 1.90 (m, 2 H), 2.58 - 2.68 (m, 2 H), 2.76 (q, J=7.5 Hz, 2 H), 3.58 - 3.68 (m, 2 H), 4.73 (t, J=7.5 Hz, 1 H), 6.54 - 6.63 (m, 3 H), 7.14 - 7.26 (m, 2 H), 7.35 - 7.40 (m, 1 H), 7.46 - 7.51 (m, 1 H), 7.54 (d, J=8.7 Hz, 2 H).

[0871]

Example A35

3-{[(4-{[cyclohexyl(6-methoxy-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0872]



[0873]

Using 4-{[cyclohexyl(6-methoxy-1-benzofuran-2-yl)methyl]amino}benzoic acid (102 mg) synthesized in Example A28(4) and in the same manner as in Example A1(4), the title object compound (40.0 mg, 33%) was obtained as a pale-red solid.

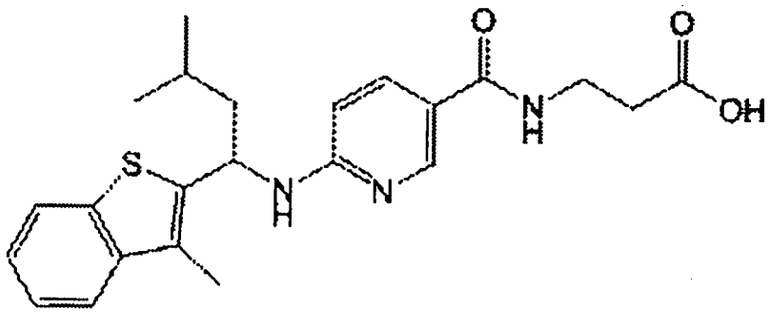
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 1.35 (m, 5 H), 1.54 - 1.84 (m, 4 H), 1.84 - 1.99 (m, 2 H), 2.55 - 2.68 (m, 2 H), 3.56 - 3.69 (m, 2 H), 3.82 (s, 3 H), 4.36 (d, J=6.4 Hz, 1 H), 6.42 (s, 1 H), 6.51 - 6.66 (m, 3 H), 6.81 (dd, J=8.5, 2.1 Hz, 1 H), 6.97 (d, J=2.1 Hz, 1 H), 7.31 (d, J=8.5 Hz, 1 H), 7.53 (d, J=8.3 Hz, 2 H).

[0874]

Example A36

3-{[(6-{[3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}pyridin-3-yl)carbonyl]amino}propanoic acid

[0875]



[0876]

(1) methyl 6-{[3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}pyridine-3-carboxylate

To a mixture of 3-methyl-1-(3-methyl-1-benzothiophen-2-

yl)butan-1-one (1.00 g) synthesized in Example A32(1), methyl 6-aminopyridine-3-carboxylate (654 mg), triethylamine (4.79 mL) and dichloromethane (20 mL) was added titanium (IV) chloride (566 μL) at 0°C, and the mixture was stirred overnight at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown solid. To a mixture of the obtained solid, acetic acid (2 mL) and tetrahydrofuran (20 mL) was added sodium cyanoborohydride (540 mg), and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give a pale-brown solid. To a mixture of the obtained solid, trifluoroacetic acid (1.00 mL) and ethanol (10 mL) was added sodium cyanoborohydride (251 mg), and the mixture was stirred at room temperature for 1 hr. In addition, sodium cyanoborohydride (251 mg) was added, and the mixture was stirred at room temperature for 30 min then at 50°C for 1 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (743 mg, 47%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 (d, J=6.3 Hz, 3 H), 1.01 (d, J=6.3 Hz, 3 H), 1.64 - 1.96 (m, 3 H), 2.48 (s, 3 H), 3.83 (s, 3 H), 5.25 - 5.40 (m, 2 H), 6.28 (d, J=8.7 Hz, 1 H), 7.24 - 7.39 (m, 2 H), 7.61 - 7.66 (m, 1 H), 7.71 - 7.76 (m, 1 H), 7.91 (dd, J=8.7, 2.0 Hz, 1 H), 8.73 (d, J=2.0 Hz, 1 H).

(2) 6-{[3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}pyridine-3-carboxylic acid

Using methyl 6-{[3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}pyridine-3-carboxylate (743 mg) synthesized above and in the same manner as in Example A23(4), the title object compound (236 mg, 33%) was obtained as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 0.99 (m, 6 H), 1.58 - 1.78 (m, 2 H), 1.81 - 1.95 (m, 1 H), 2.44 (s, 3 H), 5.51 - 5.64 (m, 1 H), 6.53 (d, J=8.7 Hz, 1 H), 7.24 - 7.38 (m, 2 H), 7.67 (d, J=8.1 Hz, 1 H), 7.73 - 7.92 (m, 3 H), 8.50 (d, J=2.4 Hz, 1 H), 12.29 (br s, 1 H).

(3) 3-{[(6-{[3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}pyridin-3-yl)carbonyl]amino}propanoic acid

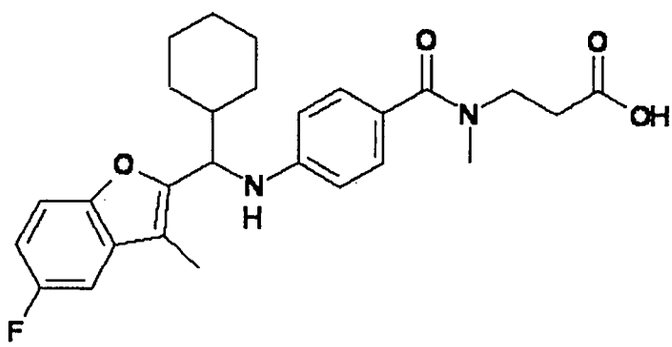
Using 6-{[3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}pyridine-3-carboxylic acid (115 mg) synthesized above and in the same manner as in Example A1(4), the title object compound (112 mg, 81%) was obtained as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 (d, J=6.0 Hz, 3 H), 1.03 (d, J=6.2 Hz, 3 H), 1.71 - 1.85 (m, 2 H), 1.95 - 2.11 (m, 1 H), 2.49 (s, 3 H), 2.57 - 2.67 (m, 2 H), 3.67 - 3.79 (m, 2 H), 4.86 - 4.98 (m, 1 H), 6.48 (d, J=9.2 Hz, 1 H), 7.24 - 7.33 (m, 1 H), 7.33 - 7.41 (m, 1 H), 7.61 - 7.75 (m, 3 H), 8.10 - 8.20 (m, 2 H), 8.87 - 8.97 (m, 1 H).

[0877]

Example A37

3-{[(4-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0878]



[0879]

(1) 5-fluoro-N-methoxy-N,3-dimethyl-1-benzofuran-2-carboxamide

To a mixture of 1-(5-fluoro-2-hydroxyphenyl)ethanone (10.0 g), 2-chloro-N-methoxy-N-methylacetamide (9.82 g), sodium iodide (19.5 g) and N,N-dimethylformamide (200 mL) was added potassium carbonate (18.0 g), and the mixture was stirred at 80°C overnight. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a brown solid. To a solution (200 mL) of the obtained solid in N,N-dimethylformamide was added 1,8-diazabicyclo[5.4.0]undec-7-ene (9.71 mL), and the mixture was stirred at 120°C for 4 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:3, volume ratio) to give the title object compound (4.37 g, 28%) as a brown oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.47 (s, 3 H), 3.38 (s, 3 H), 3.86 (s, 3 H), 6.98 - 7.16 (m, 1 H), 7.21 - 7.27 (m, 1 H), 7.37 - 7.43 (m, 1 H).

(2) cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methanol

To a solution (80 mL) of 5-fluoro-N-methoxy-N,3-dimethyl-1-benzofuran-2-carboxamide (4.37 g) synthesized above in tetrahydrofuran was added dropwise 1.5M diisobutylaluminum hydride toluene solution (24.5 mL) at 0°C, and the mixture was stirred for 1 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:9, volume ratio) to give a pale-brown solid. To a solution (50 mL) of the obtained solid in

tetrahydrofuran was added dropwise 1.0M cyclohexylmagnesium bromide tetrahydrofuran solution (21.8 mL) at 0°C, and the mixture was stirred for 1 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=3:17, volume ratio) to give the title object compound (1.32 g, 27%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 - 1.43 (m, 6 H), 1.61 - 1.71 (m, 2 H), 1.75 - 1.98 (m, 3 H), 2.09 - 2.21 (m, 4 H), 4.51 (dd, J=8.4, 6.0 Hz, 1 H), 6.92 - 7.00 (m, 1 H), 7.08 - 7.13 (m, 1 H), 7.30 - 7.36 (m, 1 H).

(3) 2-[chloro(cyclohexyl)methyl]-5-fluoro-3-methyl-1-benzofuran

Using cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methanol (1.01 g) synthesized above and in the same manner as in Example A11(3), the title object compound (900 mg, 83%) was obtained as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.83 - 1.40 (m, 5 H), 1.40 - 1.50 (m, 1 H), 1.60 - 1.72 (m, 2 H), 1.77 - 1.88 (m, 1 H), 2.10 - 2.25 (m, 4 H), 2.28 - 2.38 (m, 1 H), 4.79 (d, J=9.6 Hz, 1 H), 6.96 - 7.04 (m, 1 H), 7.09 - 7.14 (m, 1 H), 7.34 - 7.39 (m, 1 H).

(4) 3-{[(4-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

Using 2-[chloro(cyclohexyl)methyl]-5-fluoro-3-methyl-1-benzofuran (400 mg) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (355 mg) synthesized in Example 2(2) and in the same manner as in Example A22(4), the title object compound (303 mg, 46%) was obtained as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.37 (m, 5 H), 1.45 - 1.56 (m, 1 H), 1.60 - 1.97 (m, 4 H), 2.03 - 2.14 (m, 1 H), 2.22 (s,

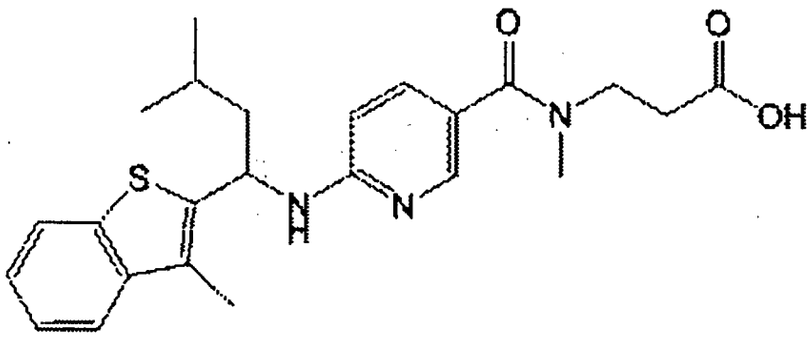
3 H), 2.64 (t, J=6.5 Hz, 2 H), 3.02 (s, 3 H), 3.69 (t, J=6.5 Hz, 2 H), 4.36 (d, J=7.9 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.88 - 6.97 (m, 1 H), 7.07 (dd, J=8.5, 2.6 Hz, 1 H), 7.23 (d, J=8.7 Hz, 2 H), 7.25 - 7.31 (m, 1 H).

[0880]

Example A38

3-{methyl[(6-{[3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}pyridin-3-yl)carbonyl]amino}propanoic acid

[0881]




[0882]

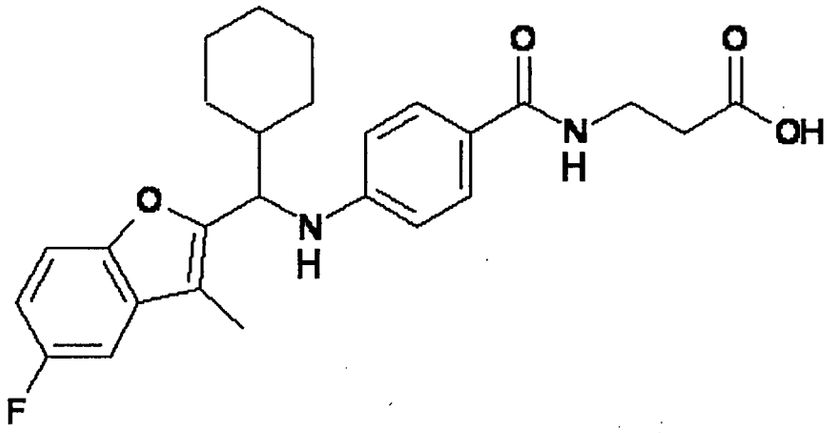
Using 6-{[3-methyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}pyridine-3-carboxylic acid (121 mg) synthesized in Example A36(2) and ethyl 3-(methylamino)propanoate (67.2 mg) and in the same manner as in Example A1(4), the title object compound (115 mg, 77%) was obtained as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 (d, J=6.2 Hz, 3 H), 1.01 (d, J=6.4 Hz, 3 H), 1.67 - 1.86 (m, 2 H), 1.93 - 2.08 (m, 1 H), 2.47 (s, 3 H), 2.62 - 2.71 (m, 2 H), 3.08 (s, 3 H), 3.67 - 3.84 (m, 2 H), 4.84 - 4.95 (m, 1 H), 6.35 (d, J=8.9 Hz, 1 H), 7.24 - 7.31 (m, 1 H), 7.32 - 7.39 (m, 1 H), 7.51 - 7.59 (m, 1 H), 7.64 (d, J=7.7 Hz, 1 H), 7.73 (d, J=7.7 Hz, 1 H), 8.05 - 8.17 (m, 1 H).

[0883]

Example A39

3-{[(4-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0884]



[0885]

Using 2-[chloro(cyclohexyl)methyl]-5-fluoro-3-methyl-1-benzofuran (400 mg) synthesized in Example A37(3) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (336 mg) synthesized in Example 1(2) and in the same manner as in Example A22(4), the title object compound (321 mg, 50%) was obtained as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 - 1.36 (m, 5 H), 1.43 - 1.56 (m, 1 H), 1.59 - 1.95 (m, 4 H), 2.00 - 2.12 (m, 1 H), 2.20 (s, 3 H), 2.59 (t, J=5.7 Hz, 2 H), 3.55 - 3.67 (m, 2 H), 4.37 (d, J=8.1 Hz, 1 H), 6.54 (d, J=8.8 Hz, 2 H), 6.71 (t, J=6.0 Hz, 1 H), 6.87 - 6.95 (m, 1 H), 7.05 (dd, J=8.5, 2.4 Hz, 1 H), 7.21 - 7.30 (m, 1 H), 7.52 (d, J=8.8 Hz, 2 H).

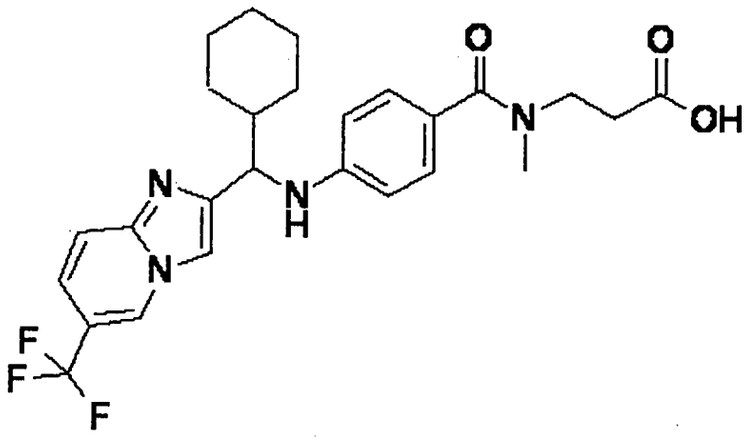
[0886]

Example A40

3-[{[4-({cyclohexyl[6-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0887]

372



[0888]

(1) 6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carbaldehyde

To a solution of 5-(Trifluoromethyl)pyridin-2-amine (12.9 g) was dissolved in dimethoxyethane (150 mL) was added 1,1,3-trichloroacetone (12.7 mL) at room temperature, and the mixture was stirred overnight. The precipitated solid was collected, and suspended in ethanol (50 mL), and the mixture was heated under reflux for 3 hr. After allowing to cool to room temperature, the solvent was evaporated under reduced pressure, saturated aqueous sodium hydrogen carbonate was added to the residue, and the mixture was extracted with ethyl acetate-tetrahydrofuran (1:1, volume ratio). The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give 2-(dichloromethyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine (10.3 g) as a white solid. The obtained solid was suspended in a mixed solvent of water (100 mL) and tetrahydrofuran (20 mL), and calcium carbonate (8.0 g) was added to the mixture at room temperature, and the mixture was stirred at 100°C for 1 hr. The mixture was allowed to cool to room temperature, the insoluble material was filtered off, and the filtrate was extracted with ethyl acetate. The extract was dried over magnesium sulfate, and concentrated under reduced pressure to give a white solid. The

residue was washed with diisopropyl ether to give the title object compound (7.3 g, 43%) as white crystals.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 7.43 (d, J=9.8 Hz, 1 H), 7.82 (d, J=9.8 Hz, 1H), 8.26 (s, 1 H), 8.58 (s, 1 H), 10.19 (s, 1 H).

(2) cyclohexyl[6-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl]methanol

To a solution of 6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carbaldehyde (2.1 g) synthesized above in tetrahydrofuran (40 mL) was added dropwise cyclohexylmagnesium bromide (1M tetrahydrofuran solution, 15 mL) at 0°C. After stirring at 0°C for 1 hr, aqueous ammonium chloride solution was added. The mixture was extracted with ethyl acetate, and the solvent was evaporated under reduced pressure. The precipitate was washed with ethanol-diisopropyl ether to give the title object compound (0.9 g, 30%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.01 - 1.96 (m, 11 H), 2.43 (d, J=6.1 Hz, 1 H), 4.66 (t, J=5.9 Hz, 1 H), 7.31 (d, J=9.8 Hz, 1 H), 7.59 (s, 1 H), 7.66 (d, J=9.8 Hz, 1 H), 8.46 (s, 1 H).

(3) 3-[{[4-({cyclohexyl[6-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

Using cyclohexyl[6-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl]methanol (1.1 g) synthesized above and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.94 g) synthesized in Example 2(2) and in the same manner as in Example 4, the title object compound (3.0 mg, 2%) was obtained as an oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 - 2.16 (m, 11 H), 2.50 - 2.75 (m, 2 H), 3.06 (s, 3 H), 3.10 - 3.25 (br s, 1 H), 3.61 - 3.82 (m, 2 H), 4.43 (d, J=6.0 Hz, 1 H), 6.54 (d, J=9.0 Hz, 2 H), 7.16 (d, J=9.0 Hz, 2 H), 7.45 (d, J=9.0 Hz, 1 H), 7.63 (s, 1 H), 7.84 (d, J=9.0 Hz, 1 H), 8.53 (s, 1 H).

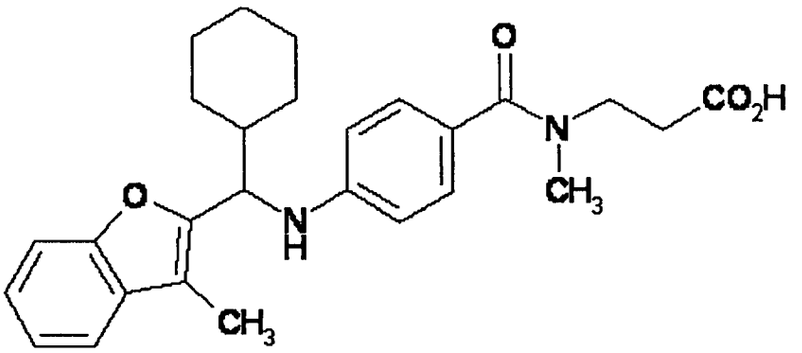
[0889]

Example A41

3-{[(4-{[cyclohexyl(3-methyl-1-benzofuran-2-

yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0890]



[0891]

Ethyl 3-{[(4-{[cyclohexyl(3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (9.85 g) synthesized in Example A16 was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase:hexane/ethanol (500/500), flow rate: 60 mL/min, column temperature: room temperature). The fraction containing an optically active form having a shorter retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (4.85 g, 99.9% ee). To a mixture of the obtained amorphous form, ethanol (20 mL) and tetrahydrofuran (20 mL) was added 1N lithium hydroxide (22 mL), and the mixture was stirred at room temperature for 1 hr and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (20 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (4.41 g, 97%,99.9% ee) as a white solid. The obtained white solid (50 mg) was crystallized from ethanol/water to give ethanol-containing crystals (41 mg). The ethanol-containing crystals (35 mg) were recrystallized from diethyl ether to give colorless crystal (18 mg) free of solvent.

$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.97 - 1.28 (m, 5 H) 1.30 -

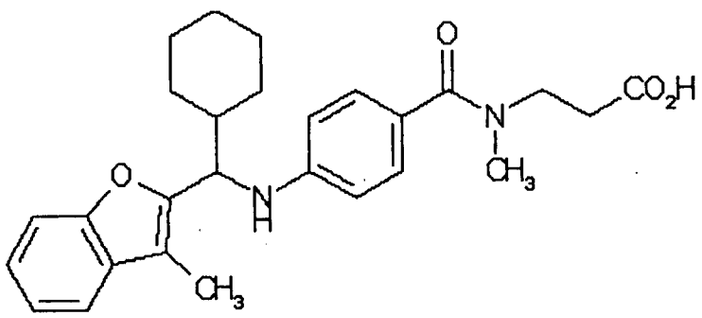
1.39 (m, 1 H) 1.52 - 1.81 (m, 3 H) 1.81 - 2.00 (m, 1 H) 2.03 - 2.18 (m, 1 H) 2.26 (s, 3 H) 2.40 - 2.49 (m, 2 H) 2.88 (s, 3 H) 3.50 (t, J=7.38 Hz, 2 H) 4.41 (t, J=8.33 Hz, 1 H) 6.48 (d, J=7.95 Hz, 1 H) 6.60 (d, J=8.71 Hz, 2 H) 7.09 (d, J=8.33 Hz, 2 H) 7.14 - 7.29 (m, 2 H) 7.36 - 7.55 (m, 2 H) 12.27 (brs, 1 H).

[0892]

Example A42

3-{[(4-{[cyclohexyl(3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0893]



[0894]

Ethyl 3-{[(4-{[cyclohexyl(3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (9.85 g) synthesized in Example A16 was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/ethanol (500/500), flow rate: 60 mL/min, column temperature: room temperature). The fraction containing an optically active form having a longer retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (4.81 g, 99.9% ee). To a mixture of the obtained amorphous form, ethanol (20 mL) and tetrahydrofuran (20 mL) was added 1N lithium hydroxide aqueous solution (22 mL), and the mixture was stirred at room temperature for 1 hr and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (20 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the

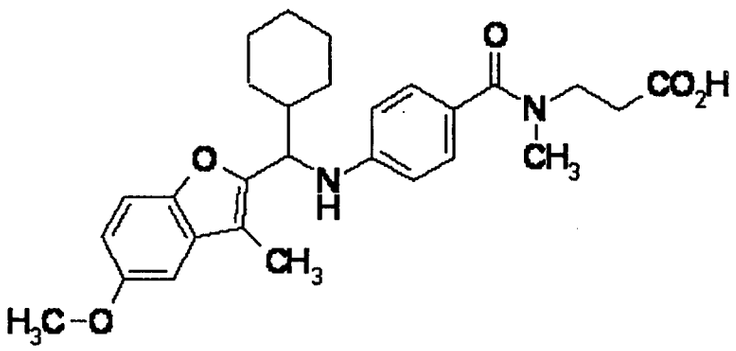
title object compound (4.43 g, 98%,99.9% ee) as a white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.97 - 1.28 (m, 5 H) 1.30 - 1.39 (m, 1 H) 1.52 - 1.81 (m, 3 H) 1.81 - 2.00 (m, 1 H) 2.03 - 2.18 (m, 1 H) 2.26 (s, 3 H) 2.40 - 2.49 (m, 2 H) 2.88 (s, 3 H) 3.50 (t, J=7.38 Hz, 2 H) 4.41 (t, J=8.33 Hz, 1 H) 6.48 (d, J=7.95 Hz, 1 H) 6.60 (d, J=8.71 Hz, 2 H) 7.09 (d, J=8.33 Hz, 2 H) 7.14 - 7.29 (m, 2 H) 7.36 - 7.55 (m, 2 H) 12.27 (brs, 1 H).

[0895]

Example A43

3-{[(4-{[cyclohexyl(5-methoxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0896]




[0897]

(1) 4-{[cyclohexyl(5-methoxy-3-methyl-1-benzofuran-2-yl)methyl]amino}benzoic acid

To a mixture of 2-[chloro(cyclohexyl)methyl]-5-methoxy-3-methyl-1-benzofuran (748 mg) synthesized in Example A27(4), methyl 4-aminobenzoate (385 mg), sodium iodide (764 mg) and N,N-dimethylformamide (15 mL) was added sodium carbonate (541 mg), and the mixture was stirred at 80°C overnight. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% ethyl acetate/hexane) to give a yellow oil. To a mixture of the obtained oil, tetrahydrofuran (20 mL) and ethanol (20 mL) was added 1N

aqueous sodium hydroxide solution (20 mL), and the mixture was stirred with heating under reflux for 5 hr, and concentrated under reduced pressure. The residue was dissolved in water (40 mL), and 1N hydrochloric acid (20 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (745 mg, 74%) as a pale-brown solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.37 (m, 5 H), 1.47 - 1.58 (m, 1 H), 1.61 - 1.98 (m, 4 H), 2.02 - 2.12 (m, 1 H), 2.24 (s, 3 H), 3.83 (s, 3 H), 4.42 (d, J=7.9 Hz, 1 H), 6.57 (d, J=8.9 Hz, 2 H), 6.83 (dd, J=8.8, 2.5 Hz, 1 H), 6.88 (d, J=2.5 Hz, 1 H), 7.26 (d, J=8.8 Hz, 1 H), 7.85 (d, J=8.9 Hz, 2 H).

[0898]

(2) ethyl 3-{[(4-{[cyclohexyl(5-methoxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[cyclohexyl(5-methoxy-3-methyl-1-benzofuran-2-yl)methyl]amino}benzoic acid (745 mg) synthesized above, ethyl 3-(methylamino)propanoate (298 mg), 1-hydroxybenzotriazole monohydrate (348 mg), triethylamine (633 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (435 mg), and the mixture was stirred at room temperature for overnight then at 50°C for 3 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (55% ethyl acetate/hexane) to give the title object compound (801 mg, 84%) as a pale-brown solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.35 (m, 8 H), 1.47 - 1.60 (m, 1 H), 1.60 - 1.97 (m, 4 H), 2.02 - 2.14 (m, 1 H), 2.22 (s, 3 H), 2.61 (t, J=7.0 Hz, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.0 Hz, 2 H), 3.84 (s, 3 H), 4.07 - 4.17 (m, 2 H), 4.30 - 4.40 (m, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.82 (dd, J=8.9, 2.6 Hz, 1 H), 6.88 (d, J=2.6 Hz, 1 H), 7.18 - 7.30 (m, 3 H).

[0899]

(3) 3-{[(4-{[cyclohexyl(5-methoxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

Ethyl 3-{[(4-{[cyclohexyl(5-methoxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (795 mg) synthesized above was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/ethanol (400/600), flow rate: 60 mL/min, column temperature: 30°C). The fraction containing an optically active form having a shorter retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (413 mg, 99.9% ee). To a mixture of the obtained amorphous form, ethanol (5 mL) and tetrahydrofuran (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (355 mg, 47%, 99.9% ee) as a white solid.

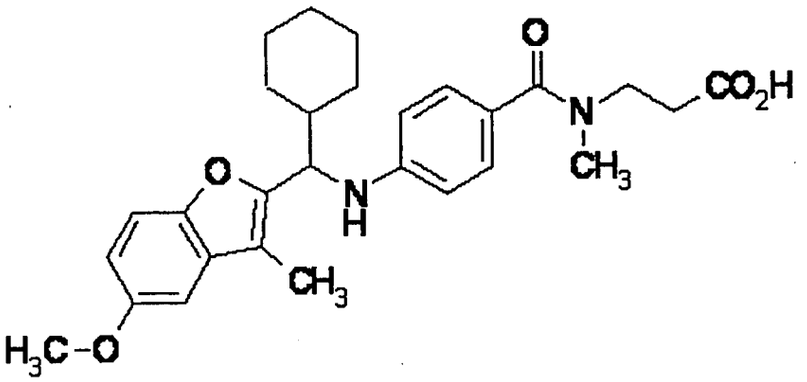
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.37 (m, 5 H), 1.47 - 1.57 (m, 1 H), 1.60 - 1.96 (m, 4 H), 2.03 - 2.13 (m, 1 H), 2.23 (s, 3 H), 2.65 (t, J=6.4 Hz, 2 H), 3.02 (s, 3 H), 3.69 (t, J=6.4 Hz, 2 H), 3.83 (s, 3 H), 4.36 (d, J=8.0 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.82 (dd, J=8.9, 2.4 Hz, 1 H), 6.88 (d, J=2.4 Hz, 1 H), 7.19 - 7.29 (m, 3 H).

[0900]

Example A44

3-{[(4-{[cyclohexyl(5-methoxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0901]



[0902]

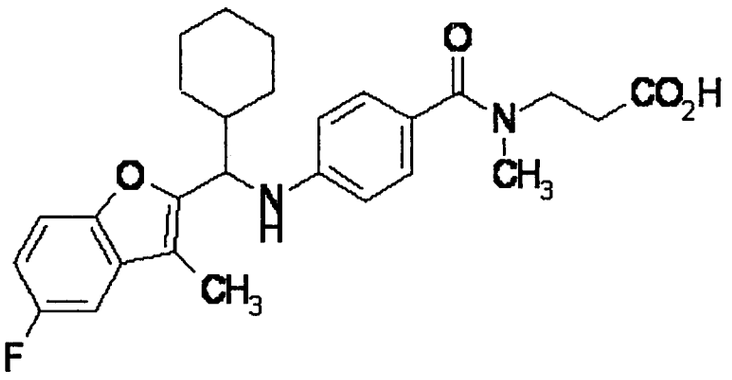
Ethyl 3-{[(4-{[cyclohexyl(5-methoxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (795 mg) synthesized in Example A43(2) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/ethanol (400/600), flow rate: 60 mL/min, column temperature: 30°C). The fraction containing an optically active form having a longer retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (418 mg, 99.9% ee). To a mixture of the obtained amorphous form, ethanol (5 mL) and tetrahydrofuran (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 1.5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (354 mg, 47%,99.9% ee) as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.37 (m, 5 H), 1.47 - 1.57 (m, 1 H), 1.60 - 1.96 (m, 4 H), 2.03 - 2.13 (m, 1 H), 2.23 (s, 3 H), 2.65 (t, J=6.4 Hz, 2 H), 3.02 (s, 3 H), 3.69 (t, J=6.4 Hz, 2 H), 3.83 (s, 3 H), 4.36 (d, J=8.0 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.82 (dd, J=8.9, 2.4 Hz, 1 H), 6.88 (d, J=2.4 Hz, 1 H), 7.19 - 7.29 (m, 3 H).

[0903]

Example A45

3-{[(4-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0904]



[0905]

(1) 4-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}benzoic acid

To a mixture of 2-[chloro(cyclohexyl)methyl]-5-fluoro-3-methyl-1-benzofuran (1.44 g) synthesized in Example A37(3), methyl 4-aminobenzoate (776 mg), sodium iodide (1.54 g) and N,N-dimethylformamide (30 mL) was added sodium carbonate (1.09 g), and the mixture was stirred at 80°C overnight. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give a yellow solid. To a mixture of the obtained solid, tetrahydrofuran (20 mL) and ethanol (20 mL) was added 1N aqueous sodium hydroxide solution (20 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (40 mL), and 1N hydrochloric acid (20 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (1.06 g, 54%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.37 (m, 5 H), 1.46 - 1.58 (m, 1 H), 1.60 - 1.99 (m, 4 H), 2.02 - 2.13 (m, 1 H), 2.23 (s,

3 H), 4.43 (d, J=8.0 Hz, 1 H), 4.51 - 4.73 (m, 1 H), 6.57 (d, J=8.7 Hz, 2 H), 6.87 - 6.98 (m, 1 H), 7.04 - 7.11 (m, 1 H), 7.24 - 7.32 (m, 1 H), 7.85 (d, J=8.7 Hz, 2 H).

[0906]

(2) ethyl 3-{[(4-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}benzoic acid (1.06 g) synthesized above, ethyl 3-(methylamino)propanoate (438 mg), 1-hydroxybenzotriazole monohydrate (512 mg), triethylamine (930 μL) and N,N-dimethylformamide (20 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (640 mg), and the mixture was stirred at room temperature for 1.5 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (55% ethyl acetate/hexane) to give the title object compound (564 mg, 41%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.37 (m, 8 H), 1.46 - 1.56 (m, 1 H), 1.61 - 1.98 (m, 4 H), 2.03 - 2.14 (m, 1 H), 2.22 (s, 3 H), 2.61 (t, J=7.0 Hz, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.0 Hz, 2 H), 4.06 - 4.17 (m, 2 H), 4.28 - 4.41 (m, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.88 - 6.97 (m, 1 H), 7.04 - 7.09 (m, 1 H), 7.22 (d, J=8.7 Hz, 2 H), 7.25 - 7.31 (m, 1 H).

[0907]

(3) 3-{[(4-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

Ethyl 3-{[(4-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (564 mg) synthesized above was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd.,

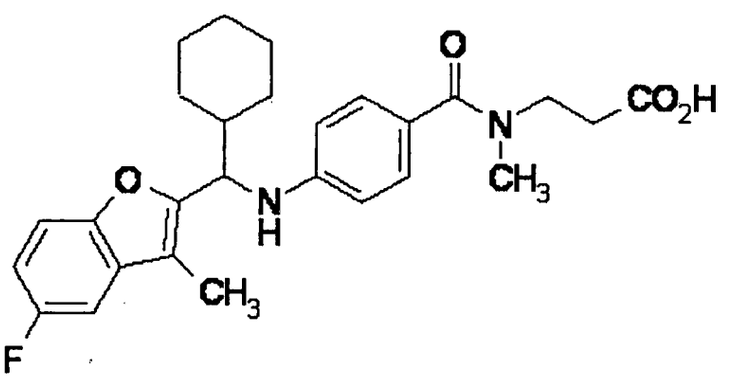
mobile phase: hexane/ethanol (400/600), flow rate: 60 mL/min, column temperature: 30°C). The fraction containing an optically active form having a shorter retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (274 mg, 99.9% ee). To a mixture of the obtained amorphous form, ethanol (5 mL) and tetrahydrofuran (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 1.5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (249 mg, 47%,99.9% ee) as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.37 (m, 5 H), 1.45 - 1.56 (m, 1 H), 1.60 - 1.97 (m, 4 H), 2.03 - 2.14 (m, 1 H), 2.22 (s, 3 H), 2.64 (t, J=6.5 Hz, 2 H), 3.02 (s, 3 H), 3.69 (t, J=6.5 Hz, 2 H), 4.36 (d, J=7.9 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.88 - 6.97 (m, 1 H), 7.07 (dd, J=8.5, 2.6 Hz, 1 H), 7.23 (d, J=8.7 Hz, 2 H), 7.25 - 7.31 (m, 1 H).

[0908]

Example A46

3-{[(4-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0909]




[0910]

Ethyl 3-{[(4-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

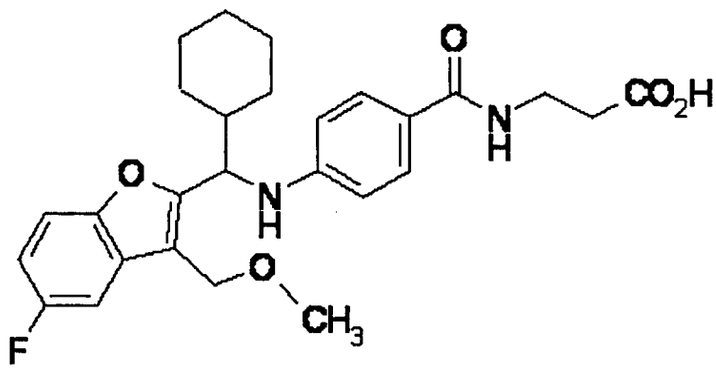
(564 mg) synthesized in Example A45(2) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase:hexane/ethanol (400/600), flow rate: 60 mL/min, column temperature: 30°C). The fraction containing an optically active form having a longer retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (273 mg, 99.9% ee). To a mixture of the obtained amorphous form, ethanol (5 mL) and tetrahydrofuran (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 1.5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (248 mg, 47%, 99.9% ee) as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.37 (m, 5 H), 1.45 - 1.56 (m, 1 H), 1.60 - 1.97 (m, 4 H), 2.03 - 2.14 (m, 1 H), 2.22 (s, 3 H), 2.64 (t, J=6.5 Hz, 2 H), 3.02 (s, 3 H), 3.69 (t, J=6.5 Hz, 2 H), 4.36 (d, J=7.9 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.88 - 6.97 (m, 1 H), 7.07 (dd, J=8.5, 2.6 Hz, 1 H), 7.23 (d, J=8.7 Hz, 2 H), 7.25 - 7.31 (m, 1 H).

[0911]

Example A47

3-({[4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

[0912]



[0913]

(1) methyl 5-fluoro-3-methyl-1-benzofuran-2-carboxylate

To a mixture of 1-(5-fluoro-2-hydroxyphenyl)ethanone (100 g), methyl bromoacetate (67.6 mL) and N,N-dimethylformamide (500 mL) was added potassium carbonate (135 g), and the mixture was stirred at 50°C for 2 hr. The insoluble material was filtered off, 1,8-diazabicyclo[5.4.0]undec-7-ene (97.1 mL) was added, and the mixture was stirred at 120°C for 30 min. 1N Hydrochloric acid was added to the reaction mixture at 0°C, and the resulting precipitate was collected by filtration to give the title object compound (77.9 g, 58%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.56 (s, 3 H), 3.99 (s, 3 H), 7.14 - 7.22 (m, 1 H), 7.24 - 7.30 (m, 1 H), 7.45 - 7.51 (m, 1 H).

[0914]

(2) methyl 3-(bromomethyl)-5-fluoro-1-benzofuran-2-carboxylate

To a solution (150 mL) of methyl 5-fluoro-3-methyl-1-benzofuran-2-carboxylate (15.4 g) synthesized above in acetonitrile were added N-bromosuccinimide (19.8 g) and 2,2'-azobis(isobutyronitrile) (1.21 g), and the mixture was stirred under argon atmosphere at 50°C for 2.5 days. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (20 - 30% ethyl acetate/hexane) to give a white solid. The obtained solid was washed with hexane to give the title object compound (15.1 g, 71%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 4.02 (s, 3 H), 4.96 (s, 2 H), 7.18 - 7.27 (m, 1 H), 7.41 - 7.47 (m, 1 H), 7.49 - 7.55 (m, 1 H).

[0915]

(3) methyl 5-fluoro-3-(methoxymethyl)-1-benzofuran-2-carboxylate

To a solution (50 mL) of methyl 3-(bromomethyl)-5-fluoro-1-benzofuran-2-carboxylate (5.87 g) synthesized above in

methanol was added 28% solution (8.33 mL) of sodium methoxide in methanol, and the mixture was stirred with heating under reflux for 3 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% ethyl acetate/hexane) to give the title object compound (3.04 g, 63%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.44 (s, 3 H), 3.99 (s, 3 H), 4.99 (s, 2 H), 7.18 (td, J=9.1, 2.7 Hz, 1 H), 7.46 - 7.52 (m, 1 H), 7.53 - 7.58 (m, 1 H).

[0916]

(4) 5-fluoro-3-(methoxymethyl)-1-benzofuran-2-carbaldehyde

To a mixture of methyl 5-fluoro-3-(methoxymethyl)-1-benzofuran-2-carboxylate (5.01 g) synthesized above, calcium chloride (4.66 g), ethanol (50 mL) and tetrahydrofuran (50 mL) was added at 0°C sodium borohydride (3.18 g), and the mixture was stirred at room temperature for 3 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, the organic solvent was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a colorless oil. To a mixture of the obtained oil, 4-methylmorpholine N-oxide (3.69 g) and acetonitrile (50 mL) was added tetrapropylammonium perruthenate (738 mg) at 0°C, and the mixture was stirred for 1.5 hr and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 20% ethyl acetate/hexane) to give the title object compound (2.33 g, 53%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.49 (s, 3 H), 4.94 (s, 2 H), 7.21 - 7.29 (m, 1 H), 7.47 - 7.54 (m, 2 H), 10.08 (s, 1 H).

[0917]

(5) cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-

yl]methanone

To a solution (20 mL) of 5-fluoro-3-(methoxymethyl)-1-benzofuran-2-carbaldehyde (1.07 g) synthesized above in tetrahydrofuran was added a 1.0M solution (7.71 mL) of cyclohexylmagnesium bromide in tetrahydrofuran at 0°C, and the mixture was stirred for 1 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, tetrahydrofuran was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 - 50% ethyl acetate/hexane) to give a pale-yellow oil. To a mixture of the obtained oil, 4-methylmorpholine N-oxide (841 mg) and acetonitrile (20 mL) was added tetrapropylammonium perruthenate (126 mg), and the mixture was stirred at room temperature for 1.5 hr and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 20% ethyl acetate/hexane) to give the title object compound (857 mg, 57%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.15 - 1.55 (m, 5 H), 1.69 - 1.80 (m, 1 H), 1.80 - 2.02 (m, 4 H), 3.25 - 3.39 (m, 1 H), 3.44 (s, 3 H), 5.00 (s, 2 H), 7.15 - 7.23 (m, 1 H), 7.43 - 7.49 (m, 1 H), 7.57 - 7.62 (m, 1 H).

[0918]

(6) methyl 4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)benzoate

To a mixture of cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methanone (857 mg) synthesized above, methyl 4-aminobenzoate (491 mg), triethylamine (3.29 mL) and methylene chloride (10 mL) was added titanium (IV) chloride (388 μL), and the mixture was stirred under argon atmosphere at room temperature overnight. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, methylene chloride was evaporated in an evaporator, and the residue was

extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (20 mL) of the obtained oil in tetrahydrofuran were added acetic acid (847 μL) and sodium cyanoborohydride (371 mg), and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 40% ethyl acetate/hexane) to give the title object compound (454 mg, 36%) as a pale-brown oil

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 - 1.36 (m, 5 H), 1.43 - 1.54 (m, 1 H), 1.60 - 1.99 (m, 4 H), 2.00 - 2.11 (m, 1 H), 3.37 (s, 3 H), 3.81 (s, 3 H), 4.48 - 4.64 (m, 4 H), 6.60 (d, J=8.8 Hz, 2 H), 6.90 - 6.99 (m, 1 H), 7.17 - 7.23 (m, 1 H), 7.28 - 7.34 (m, 1 H), 7.79 (d, J=8.8 Hz, 2 H).

[0919]

(7) 4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)benzoic acid

To a mixture of methyl 4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)benzoate (454 mg) synthesized above, tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N aqueous sodium hydroxide solution (10.0 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (10.0 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (423 mg, 96%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 1.36 (m, 5 H), 1.40 - 1.55 (m, 1 H), 1.60 - 1.99 (m, 4 H), 1.99 - 2.13 (m, 1 H), 3.38 (s, 3 H), 4.49 - 4.77 (m, 4 H), 6.61 (d, J=8.8 Hz, 2 H), 6.90 -

6.99 (m, 1 H), 7.17 - 7.23 (m, 1 H), 7.28 - 7.35 (m, 1 H), 7.84 (d, J=8.8 Hz, 2 H).

[0920]

(8) ethyl 3-({[4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}amino)propanoate

To a mixture of 4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)benzoic acid (200 mg) synthesized above, β-alanine ethyl ester hydrochloride (112 mg), 1-hydroxybenzotriazole monohydrate (112 mg), triethylamine (203 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (140 mg), and the mixture was stirred at room temperature overnight. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (207 mg, 83%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.36 (m, 8 H), 1.42 - 1.54 (m, 1 H), 1.60 - 1.97 (m, 4 H), 2.01 - 2.13 (m, 1 H), 2.58 (t, J=5.8 Hz, 2 H), 3.37 (s, 3 H), 3.61 - 3.70 (m, 2 H), 4.13 (q, J=7.1 Hz, 2 H), 4.46 - 4.62 (m, 4 H), 6.56 - 6.65 (m, 3 H), 6.90 - 6.99 (m, 1 H), 7.17 - 7.23 (m, 1 H), 7.27 - 7.33 (m, 1 H), 7.54 (d, J=8.8 Hz, 2 H).

[0921]

(9) 3-({[4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}amino)propanoic acid

To a mixture of ethyl 3-({[4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}amino)propanoate (207 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL)

was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 5 hr and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (186 mg, 95%) as a white solid.

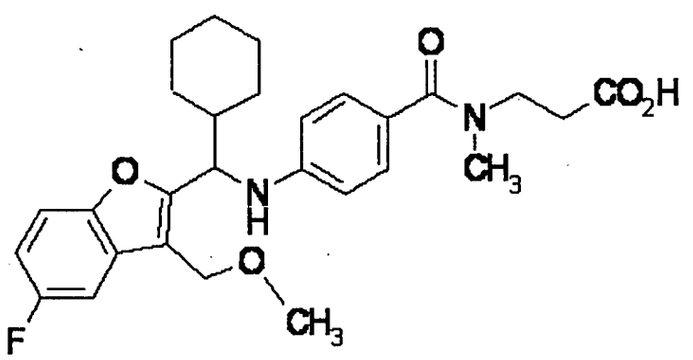
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.35 (m, 5 H), 1.41 - 1.53 (m, 1 H), 1.60 - 1.97 (m, 4 H), 2.00 - 2.11 (m, 1 H), 2.63 (t, J=5.7 Hz, 2 H), 3.37 (s, 3 H), 3.59 - 3.68 (m, 2 H), 4.50 (d, J=8.1 Hz, 1 H), 4.54 (d, J=12.2 Hz, 1 H), 4.59 (d, J=12.2 Hz, 1 H), 6.55 - 6.66 (m, 3 H), 6.90 - 6.99 (m, 1 H), 7.16 - 7.23 (m, 1 H), 7.27 - 7.34 (m, 1 H), 7.53 (d, J=8.9 Hz, 2 H).

[0922]

Example A48

3-[{[4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0923]




[0924]

(1) ethyl 3-[{[4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

To a mixture of 4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)benzoic acid (200 mg) synthesized in Example A47(7), ethyl 3-(methylamino)propanoate (95.6 mg), 1-hydroxybenzotriazole monohydrate (112 mg), triethylamine (203 μL) and N,N-

dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (140 mg), and the mixture was stirred at room temperature overnight. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (197 mg, 77%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 1.36 (m, 8 H), 1.42 - 1.53 (m, 1 H), 1.59 - 1.97 (m, 4 H), 2.02 - 2.13 (m, 1 H), 2.61 (t, J=7.0 Hz, 2 H), 3.00 (s, 3 H), 3.36 (s, 3 H), 3.70 (t, J=7.0 Hz, 2 H), 4.11 (q, J=7.1 Hz, 2 H), 4.35 - 4.51 (m, 2 H), 4.54 (d, J=12.3 Hz, 1 H), 4.59 (d, J=12.3 Hz, 1 H), 6.59 (d, J=8.5 Hz, 2 H), 6.90 - 6.99 (m, 1 H), 7.17 - 7.24 (m, 3 H), 7.28 - 7.34 (m, 1 H).

[0925]

(2) 3-[{[4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a mixture of ethyl 3-[{[4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (197 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 7 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (161 mg, 87%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.36 (m, 5 H), 1.41 - 1.53 (m, 1 H), 1.59 - 1.97 (m, 4 H), 2.01 - 2.13 (m, 1 H), 2.54 -

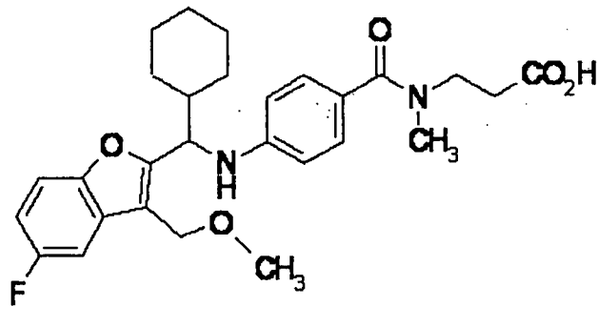
2.70 (m, 2 H), 3.01 (s, 3 H), 3.37 (s, 3 H), 3.68 (t, J=6.6 Hz, 2 H), 4.47 (d, J=7.9 Hz, 1 H), 4.55 (d, J=12.2 Hz, 1 H), 4.60 (d, J=12.2 Hz, 1 H), 6.59 (d, J=8.5 Hz, 2 H), 6.89 - 7.00 (m, 1 H), 7.17 - 7.25 (m, 3 H), 7.28 - 7.35 (m, 1 H).

[0926]

Example A49

3-[{[4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0927]



[0928]

Ethyl 3-[{[4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (1.20 g) synthesized in Example A48(1) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/ethanol (200/800), flow rate: 60 mL/min, column temperature: 30°C). The fraction containing an optically active form having a shorter retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (470 mg, 99.9% ee). To a mixture of the obtained amorphous form, ethanol (5 mL) and tetrahydrofuran (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the

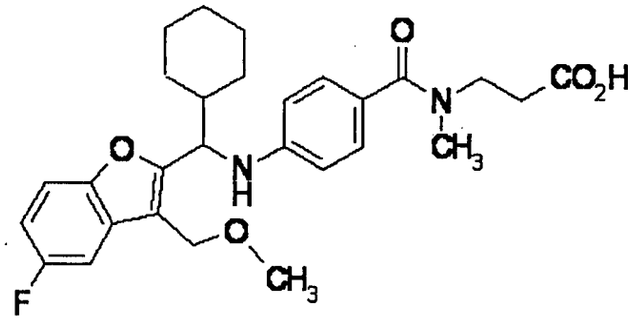
title object compound (433 mg, 38%, 99.9% ee) as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.36 (m, 5 H), 1.41 - 1.53 (m, 1 H), 1.59 - 1.97 (m, 4 H), 2.01 - 2.13 (m, 1 H), 2.54 - 2.70 (m, 2 H), 3.01 (s, 3 H), 3.37 (s, 3 H), 3.68 (t, J=6.6 Hz, 2 H), 4.47 (d, J=7.9 Hz, 1 H), 4.55 (d, J=12.2 Hz, 1 H), 4.60 (d, J=12.2 Hz, 1 H), 6.59 (d, J=8.5 Hz, 2 H), 6.89 - 7.00 (m, 1 H), 7.17 - 7.25 (m, 3 H), 7.28 - 7.35 (m, 1 H).

[0929]

Example A50

3-[{[4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[0930]




[0931]

Ethyl 3-[{[4-({cyclohexyl[5-fluoro-3-(methoxymethyl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (1.20 g) synthesized in Example A48(1) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/ethanol (200/800), flow rate: 60 mL/min, column temperature: 30°C). The fraction containing an optically active form having a longer retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (465 mg, 99.9% ee). To a mixture of the obtained amorphous form, ethanol (5 mL) and tetrahydrofuran (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was

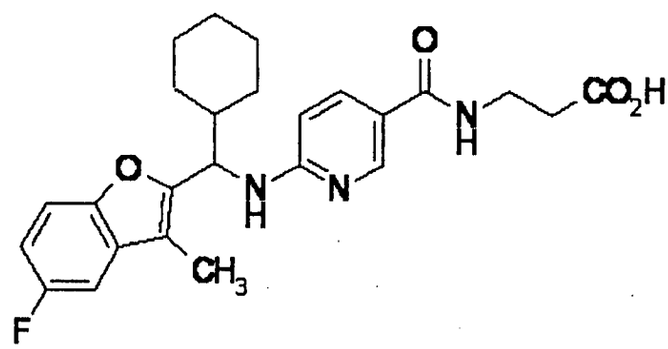
stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (415 mg, 37%, 99.9% ee) as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.36 (m, 5 H), 1.41 - 1.53 (m, 1 H), 1.59 - 1.97 (m, 4 H), 2.01 - 2.13 (m, 1 H), 2.54 - 2.70 (m, 2 H), 3.01 (s, 3 H), 3.37 (s, 3 H), 3.68 (t, J=6.6 Hz, 2 H), 4.47 (d, J=7.9 Hz, 1 H), 4.55 (d, J=12.2 Hz, 1 H), 4.60 (d, J=12.2 Hz, 1 H), 6.59 (d, J=8.5 Hz, 2 H), 6.89 - 7.00 (m, 1 H), 7.17 - 7.25 (m, 3 H), 7.28 - 7.35 (m, 1 H).

[0932]

Example A51

3-{[(6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-yl)carbonyl]amino}propanoic acid

[0933]



[0934]

(1) 2-bromo-1-cyclohexylethanone

To a solution (50 mL) of 1-cyclohexylethanone (25.0 g) in methanol was added bromine (10.1 mL) at 0°C, and the mixture was stirred at room temperature for 30 min. Saturated sodium sulfite aqueous solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 10% ethyl acetate/hexane) to give the title object compound (25.8 g,

63%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.10 - 1.50 (m, 5 H), 1.62 - 1.73 (m, 1 H), 1.75 - 1.94 (m, 4 H), 2.64 - 2.79 (m, 1 H), 3.97 (s, 2 H).

[0935]

(2) cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methanone

To a mixture of 5'-fluoro-2'-hydroxyacetophenone (5.00 g), 2-bromo-1-cyclohexylethanone (7.98 g) synthesized above and N,N-dimethylformamide (50 mL) was added potassium carbonate (13.4 g), and the mixture was stirred at room temperature overnight. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 20% ethyl acetate/hexane) to give the title object compound (5.38 g, 64%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.19 - 1.57 (m, 5 H), 1.70 - 2.01 (m, 5 H), 2.56 (s, 3 H), 3.25 - 3.36 (m, 1 H), 7.15 - 7.23 (m, 1 H), 7.24 - 7.30 (m, 1 H), 7.42 - 7.48 (m, 1 H).

[0936]

(3) methyl 6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridine-3-carboxylate

To a mixture of cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methanone (3.00 g) synthesized above, methyl 6-aminopyridine-3-carboxylate (1.93 g), triethylamine (12.8 mL) and methylene chloride (40 mL) was added a 1.0M solution (13.8 mL) of titanium (IV) chloride in methylene chloride at 0°C, and the mixture was stirred under an argon atmosphere at room temperature for 1.5 days. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, methylene chloride was removed by an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil.

To a mixture of the obtained oil, ethanol (40 mL) and tetrahydrofuran (20 mL) were added acetic acid (3.29 mL) and sodium cyanoborohydride (3.61 g), and the mixture was stirred at room temperature for 3 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, the organic solvent was removed by an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 30% ethyl acetate/hexane) to give the title object compound (547 mg, 12%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.82 - 1.35 (m, 5 H), 1.44 - 1.55 (m, 1 H), 1.56 - 1.86 (m, 3 H), 1.85 - 2.10 (m, 2 H), 2.24 (s, 3 H), 3.83 (s, 3 H), 5.02 - 5.14 (m, 1 H), 5.42 (d, J=8.2 Hz, 1 H), 6.33 (d, J=8.8 Hz, 1 H), 6.88 - 6.97 (m, 1 H), 7.04 - 7.10 (m, 1 H), 7.26 - 7.32 (m, 1 H), 7.90 (dd, J=8.8, 2.4 Hz, 1 H), 8.72 (d, J=2.4 Hz, 1 H).

[0937]

(4) 6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridine-3-carboxylic acid

To a mixture of methyl 6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridine-3-carboxylate (547 mg) synthesized above, ethanol (10 mL) and tetrahydrofuran (10 mL) was added 1N aqueous sodium hydroxide solution (10 mL), and the mixture was stirred overnight with heating under reflux. In addition, 1N aqueous sodium hydroxide solution (5.00 mL) was added, and the mixture was stirred with heating under reflux for 5 hr, and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (15 mL) was added at 0°C. The resulting precipitate was collected by filtration, and the obtained pale-brown solid was dissolved in ethyl acetate. The solution was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object

compound (478 mg, 90%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 - 1.41 (m, 5 H), 1.48 - 1.84 (m, 4 H), 2.01 - 2.18 (m, 2 H), 2.23 (s, 3 H), 4.47 - 4.65 (m, 1 H), 6.34 (d, J=8.8 Hz, 1 H), 6.87 - 6.97 (m, 1 H), 7.03 - 7.10 (m, 1 H), 7.26 - 7.33 (m, 1 H), 8.08 (d, J=8.8 Hz, 1 H), 8.70 - 8.74 (m, 1 H).

[0938]

(5) ethyl 3-{[(6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-yl)carbonyl]amino}propanoate

To a mixture of 6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridine-3-carboxylic acid (300 mg) synthesized above, β-alanine ethyl ester hydrochloride (181 mg), 1-hydroxybenzotriazole monohydrate (181 mg), triethylamine (328 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (226 mg), and the mixture was stirred at room temperature overnight. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (366 mg, 97%) as a pale-brown oil

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.36 (m, 8 H), 1.43 - 1.55 (m, 1 H), 1.57 - 1.85 (m, 3 H), 1.85 - 2.08 (m, 2 H), 2.24 (s, 3 H), 2.60 (t, J=5.9 Hz, 2 H), 3.62 - 3.72 (m, 2 H), 4.15 (q, J=7.1 Hz, 2 H), 5.01 - 5.12 (m, 1 H), 5.25 (d, J=8.8 Hz, 1 H), 6.35 (d, J=8.8 Hz, 1 H), 6.65 (t, J=6.0 Hz, 1 H), 6.88 - 6.97 (m, 1 H), 7.03 - 7.10 (m, 1 H), 7.23 - 7.31 (m, 1 H), 7.75 (dd, J=8.8, 2.5 Hz, 1 H), 8.48 (d, J=2.5 Hz, 1 H).

[0939]

(6) 3-{[(6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-yl)carbonyl]amino}propanoic acid

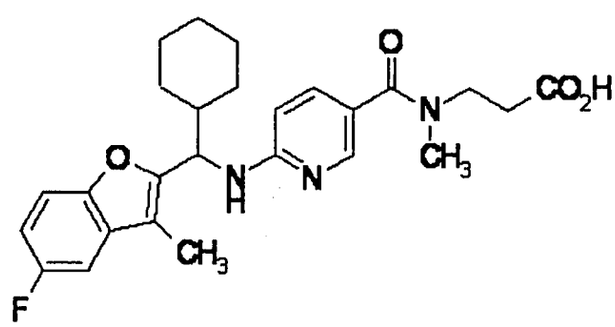
To a mixture of ethyl 3-{[(6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-yl)carbonyl]amino}propanoate (366 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature overnight, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (287 mg, 83%) as a white solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 - 1.41 (m, 5 H), 1.44 - 1.55 (m, 1 H), 1.59 - 1.84 (m, 3 H), 1.97 - 2.15 (m, 2 H), 2.23 (s, 3 H), 2.55 - 2.69 (m, 2 H), 3.65 - 3.78 (m, 2 H), 4.46 (t, J=7.8 Hz, 1 H), 6.48 (d, J=9.1 Hz, 1 H), 6.89 - 6.99 (m, 1 H), 7.04 - 7.11 (m, 1 H), 7.27 - 7.35 (m, 1 H), 7.51 - 7.61 (m, 1 H), 8.13 (dd, J=9.1, 2.1 Hz, 1 H), 8.22 (d, J=2.1 Hz, 1 H), 8.25 - 8.41 (m, 1 H).

[0940]

Example A52

3-{[(6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-yl)carbonyl](methyl)amino}propanoic acid

[0941]




[0942]

(1) ethyl 3-{[(6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-yl)carbonyl](methyl)amino}propanoate

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To a mixture of 6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridine-3-carboxylic acid (294 mg) synthesized in Example A51(4), ethyl 3-(methylamino)propanoate (151 mg), 1-hydroxybenzotriazole monohydrate (176 mg), triethylamine (322 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (221 mg), and the mixture was stirred at room temperature overnight. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (236 mg, 62%) as a pale-brown solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.34 (m, 8 H), 1.45 - 1.57 (m, 1 H), 1.58 - 1.83 (m, 3 H), 1.84 - 2.09 (m, 2 H), 2.23 (s, 3 H), 2.63 (t, J=7.0 Hz, 2 H), 3.05 (s, 3 H), 3.72 (t, J=7.0 Hz, 2 H), 4.03 - 4.17 (m, 2 H), 4.97 - 5.07 (m, 1 H), 5.08 - 5.18 (m, 1 H), 6.34 (d, J=8.6 Hz, 1 H), 6.88 - 6.97 (m, 1 H), 7.04 - 7.10 (m, 1 H), 7.23 - 7.31 (m, 1 H), 7.46 (dd, J=8.6, 2.1 Hz, 1 H), 8.18 (d, J=2.1 Hz, 1 H).

[0943]

(2) 3-{[(6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-yl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-yl)carbonyl](methyl)amino}propanoate (236 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), 1N hydrochloric acid (1.00 mL) was added at 0°C, and the

mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a pale-yellow solid. The obtained solid was recrystallized from ethyl acetate/hexane to give the title object compound (143 mg, 64%) as colorless crystals.

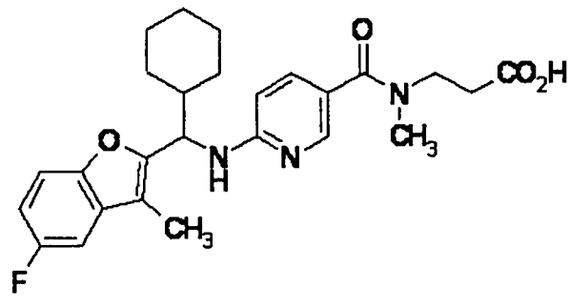
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 - 1.37 (m, 5 H), 1.38 - 1.53 (m, 1 H), 1.55 - 1.82 (m, 3 H), 1.87 - 2.12 (m, 2 H), 2.20 (s, 3 H), 2.48 - 2.68 (m, 2 H), 2.99 (br s, 3 H), 3.59 - 3.79 (m, 2 H), 4.54 - 4.76 (m, 1 H), 6.34 (d, J=8.8 Hz, 1 H), 6.86 - 6.97 (m, 1 H), 7.01 - 7.09 (m, 1 H), 7.23 - 7.34 (m, 1 H), 7.51 (d, J=8.8 Hz, 1 H), 8.11 (br s, 1 H).

[0944]

Example A53

3-{[(6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-yl)carbonyl](methyl)amino}propanoic acid

[0945]




[0946]

Ethyl 3-{[(6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-yl)carbonyl](methyl)amino}propanoate (4.06 g) synthesized in Example A52(1) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/2-propanol (700/300-200/800), flow rate: 60 mL/min-50 mL/min, column temperature: room temperature). The fraction containing an optically active form having a shorter

retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (1.94 g, 99.9% ee). To a mixture of the obtained amorphous form, ethanol (10 mL) and tetrahydrofuran (10 mL) was added 1N lithium hydroxide aqueous solution (8 mL), and the mixture was stirred at room temperature for 1 hr and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (8 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (1.81 g, 95%, 99.9% ee) as a white solid.

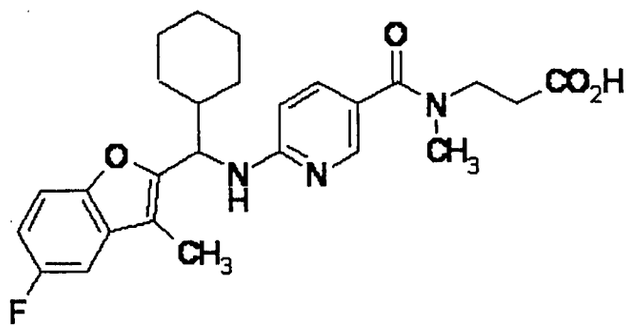
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.89 - 1.28 (m, 5 H) 1.34 (d, J=12.12 Hz, 1 H) 1.49 - 1.80 (m, 3 H) 1.80 - 2.08 (m, 2 H) 2.23 (s, 3 H) 2.50 - 2.54 (m, 2 H) 2.92 (s, 3 H) 3.53 (t, J=7.38 Hz, 2 H) 5.15 (t, J=8.90 Hz, 1 H) 6.56 (d, J=8.71 Hz, 1 H) 7.05 (td, J=9.28, 2.65 Hz, 1 H) 7.31 (dd, J=8.71, 2.65 Hz, 1 H) 7.36 - 7.56 (m, 2 H) 8.04 (d, J=2.27 Hz, 1 H) 12.22 (brs, 1 H).

[0947]

Example A54

3-{[(6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-yl)carbonyl](methyl)amino}propanoic acid

[0948]




[0949]

Ethyl 3-{[(6-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-

yl)carbonyl](methyl)amino}propanoate (4.06 g) synthesized in Example A52(1) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/2-propanol (700/300-200/800), flow rate: 60 mL/min, column temperature: room temperature). The fraction containing an optically active form having a longer retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (1.96 g, 99.9% ee). To a mixture of the obtained amorphous form, ethanol (10 mL) and tetrahydrofuran (10 mL) was added 1N lithium hydroxide aqueous solution (8 mL), and the mixture was stirred at room temperature for 1 hr and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (8 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (1.80 g, 99%,99.9% ee) as a white solid.

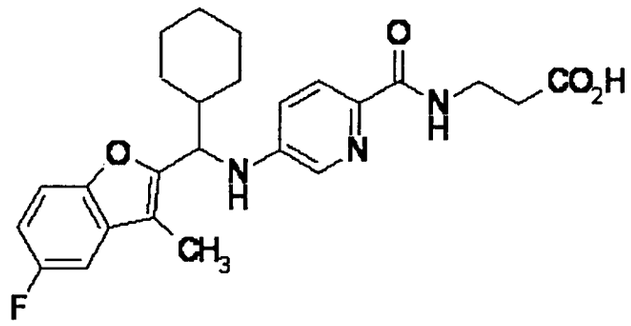
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.89 - 1.28 (m, 5 H) 1.34 (d, J=12.12 Hz, 1 H) 1.49 - 1.80 (m, 3 H) 1.80 - 2.08 (m, 2 H) 2.23 (s, 3 H) 2.50 - 2.54 (m, 2 H) 2.92 (s, 3 H) 3.53 (t, J=7.38 Hz, 2 H) 5.15 (t, J=8.90 Hz, 1 H) 6.56 (d, J=8.71 Hz, 1 H) 7.05 (td, J=9.28, 2.65 Hz, 1 H) 7.31 (dd, J=8.71, 2.65 Hz, 1 H) 7.36 - 7.56 (m, 2 H) 8.04 (d, J=2.27 Hz, 1 H) 12.22 (brs, 1 H).

[0950]

Example A55

3-{[(5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-2-yl)carbonyl]amino}propanoic acid

[0951]



[0952]

(1) methyl 5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridine-2-carboxylate

To a solution (15 mL) of cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methanol (1.50 g) synthesized in Example A37(2) in toluene was added thionyl chloride (625 μL), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into ice-cooled saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a brown oil. To a mixture of the obtained oil, methyl 5-aminopyridine-2-carboxylate (957 mg), sodium iodide (1.71 g) and N,N-dimethylformamide (15 mL) was added sodium carbonate (1.21 g), and the mixture was stirred at 80°C overnight. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 - 50% ethyl acetate/hexane) to give the title object compound (909 mg, 40%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.37 (m, 5 H), 1.46 - 1.57 (m, 1 H), 1.60 - 2.00 (m, 4 H), 2.02 - 2.14 (m, 1 H), 2.23 (s, 3 H), 3.90 (s, 3 H), 4.39 (t, J=8.2 Hz, 1 H), 4.70 (d, J=8.2 Hz, 1 H), 6.84 (dd, J=8.6, 3.0 Hz, 1 H), 6.89 - 6.97 (m, 1 H),

7.04 - 7.10 (m, 1 H), 7.22 - 7.30 (m, 1 H), 7.88 (d, J=8.6 Hz, 1 H), 8.08 (d, J=3.0 Hz, 1 H).

[0953]

(2) 5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridine-2-carboxylic acid

To a mixture of methyl 5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridine-2-carboxylate (909 mg) synthesized above, ethanol (20 mL) and tetrahydrofuran (20 mL) was added 1N aqueous sodium hydroxide solution (20 mL), and the mixture was stirred with heating under reflux for 5 hr, and concentrated under reduced pressure. 1N Hydrochloric acid (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with hexane to give the title object compound (751 mg, 86%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.39 (m, 5 H), 1.46 - 1.60 (m, 1 H), 1.62 - 2.02 (m, 4 H), 2.02 - 2.15 (m, 1 H), 2.25 (s, 3 H), 4.41 (t, J=7.9 Hz, 1 H), 4.72 - 4.83 (m, 1 H), 6.90 - 7.00 (m, 2 H), 7.07 - 7.13 (m, 1 H), 7.24 - 7.33 (m, 1 H), 7.91 - 7.98 (m, 2 H).

[0954]

(3) ethyl 3-{[(5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-2-yl)carbonyl]amino}propanoate

To a mixture of 5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridine-2-carboxylic acid (300 mg) synthesized above, β-alanine ethyl ester hydrochloride (181 mg), 1-hydroxybenzotriazole monohydrate (181 mg), triethylamine (328 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (226 mg), and the mixture was stirred at room temperature overnight. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was

washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (361 mg, 96%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.39 (m, 8 H), 1.46 - 2.00 (m, 5 H), 2.03 - 2.14 (m, 1 H), 2.24 (s, 3 H), 2.60 (t, J=6.2 Hz, 2 H), 3.64 - 3.72 (m, 2 H), 4.15 (q, J=7.1 Hz, 2 H), 4.34 - 4.42 (m, 1 H), 4.45 - 4.52 (m, 1 H), 6.86 - 6.98 (m, 2 H), 7.05 - 7.10 (m, 1 H), 7.24 - 7.30 (m, 1 H), 7.87 - 7.93 (m, 2 H), 8.06 - 8.13 (m, 1 H).

[0955]

(4) 3-{[(5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-2-yl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-2-yl)carbonyl]amino}propanoate (361 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (324 mg, 95%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.36 (m, 5 H), 1.45 - 1.56 (m, 1 H), 1.61 - 2.00 (m, 4 H), 2.01 - 2.12 (m, 1 H), 2.22 (s, 3 H), 2.65 (t, J=6.1 Hz, 2 H), 3.64 - 3.75 (m, 2 H), 4.37 (d, J=8.0 Hz, 1 H), 6.85 - 6.99 (m, 2 H), 7.03 - 7.10 (m, 1 H), 7.23 - 7.30 (m, 1 H), 7.86 - 7.94 (m, 2 H), 8.14 (t, J=6.2 Hz, 1 H).

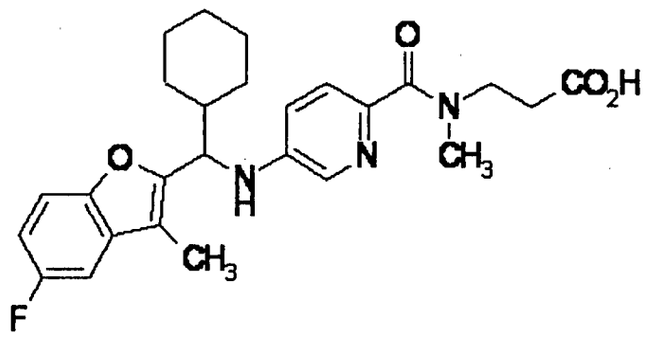
[0956]

Example A56

3-{[(5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoic

acid

[0957]



[0958]

(1) ethyl 3-{[(5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoate

To a mixture of 5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridine-2-carboxylic acid (300 mg) synthesized in Example A55(2), ethyl 3-(methylamino)propanoate (155 mg), 1-hydroxybenzotriazole monohydrate (181 mg), triethylamine (328 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (226 mg), and the mixture was stirred at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20 - 60% ethyl acetate/hexane) to give the title object compound (318 mg, 82%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.38 (m, 8 H), 1.46 - 1.57 (m, 1 H), 1.60 - 1.99 (m, 4 H), 2.03 - 2.16 (m, 1 H), 2.22 (s, 3 H), 2.63 - 2.78 (m, 2 H), 3.00 - 3.21 (m, 3 H), 3.69 - 3.87 (m, 2 H), 4.01 - 4.19 (m, 2 H), 4.32 - 4.40 (m, 1 H), 4.41 - 4.49 (m, 1 H), 6.84 - 6.98 (m, 2 H), 7.04 - 7.11 (m, 1 H),

7.24 - 7.31 (m, 1 H), 7.44 - 7.59 (m, 1 H), 7.88 - 7.95 (m, 1 H).

[0959]

(2) 3-{[(5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoate (318 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (262 mg, 87%) as a white solid.

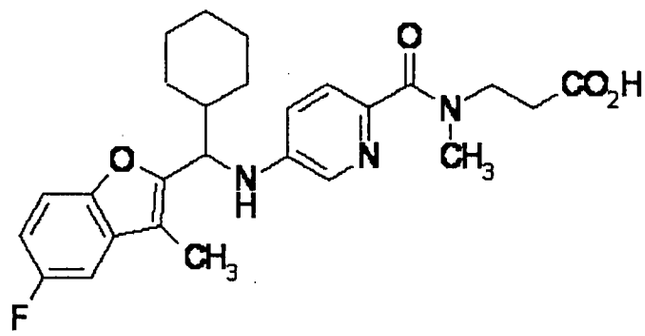
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.37 (m, 5 H), 1.46 - 1.56 (m, 1 H), 1.60 - 1.99 (m, 4 H), 2.03 - 2.13 (m, 1 H), 2.23 (s, 3 H), 2.68 - 2.89 (m, 2 H), 3.09 (br s, 3 H), 3.77 (t, J=6.8 Hz, 2 H), 4.36 (d, J=8.3 Hz, 1 H), 6.87 - 6.99 (m, 2 H), 7.05 - 7.11 (m, 1 H), 7.24 - 7.32 (m, 1 H), 7.48 - 7.66 (m, 1 H), 7.90 - 8.00 (m, 1 H).

[0960]

Example A57

3-{[(5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoic acid

[0961]



[0962]

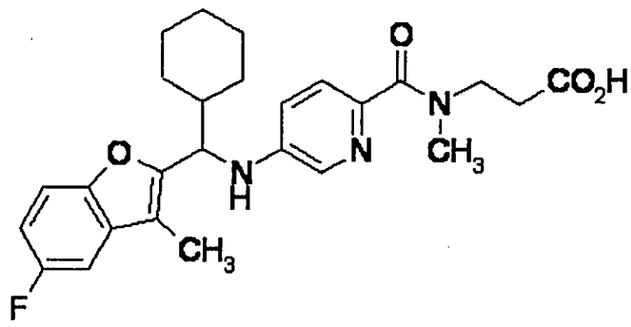
Ethyl 3-{[(5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoate (5.83 g) synthesized in Example A56(1) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/ethanol (500/500), flow rate: 60 mL/min, column temperature: room temperature). The fraction containing an optically active form having a shorter retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (2.90 g, 99.9%ee). To a mixture of the obtained amorphous form, ethanol (10 mL) and tetrahydrofuran (10 mL) was added 1N lithium hydroxide aqueous solution (12 mL), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (30 mL), and 1N hydrochloric acid (12 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (2.67 g, 99%,99.9% ee) as a white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.98 - 1.29 (m, 5 H) 1.30 - 1.39 (m, 1 H) 1.63 (brs, 2 H) 1.75 (d, J=11.36 Hz, 1 H) 1.82 - 2.00 (m, 1 H) 2.09 (d, J=11.74 Hz, 1 H) 2.25 (s, 3 H) 2.53 - 2.66 (m, 2 H) 2.88 - 3.03 (m, 3 H) 3.32 (br s, 2 H) 4.51 (t, J=8.33 Hz, 1 H) 6.80 (d, J=8.33 Hz, 1 H) 6.96 (dd, J=8.71, 2.65 Hz, 1 H) 7.05 (td, J=9.28, 2.65 Hz, 1 H) 7.26 - 7.39 (m, 2 H) 7.47 (dd, J=8.90, 3.98 Hz, 1 H) 7.95 (d, J=2.27 Hz, 1 H) 12.26 (br s, 1 H).

[0963]

Example A58

3-{[(5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoic acid

[0964]



[0965]

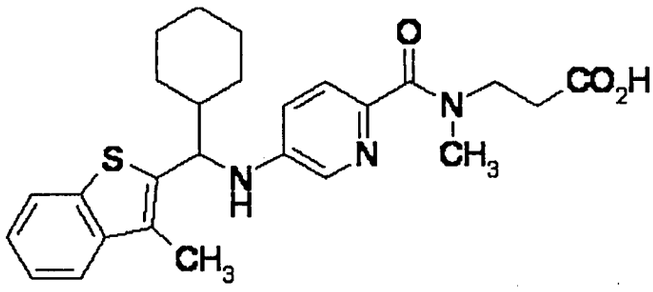
Ethyl 3-{[(5-{[cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoate (5.83 g) synthesized in Example A56(1) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/ethanol (500/500), flow rate: 60 mL/min, column temperature: room temperature). The fraction containing an optically active form having a longer retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (2.82 g, 99.9% ee). To a mixture of the obtained amorphous form, ethanol (10 mL) and tetrahydrofuran (10 mL) was added 1N lithium hydroxide aqueous solution (12 mL), and the mixture was stirred at room temperature for 1 hr and concentrated under reduced pressure. The residue was dissolved in water (30 mL), and 1N hydrochloric acid (12 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (2.64 g, 97%, 99.9% ee) as a white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.98 - 1.29 (m, 5 H) 1.30 - 1.39 (m, 1 H) 1.63 (brs, 2 H) 1.75 (d, J=11.36 Hz, 1 H) 1.82 - 2.00 (m, 1 H) 2.09 (d, J=11.74 Hz, 1 H) 2.25 (s, 3 H) 2.53 - 2.66 (m, 2 H) 2.88 - 3.03 (m, 3 H) 3.32 (br s, 2 H) 4.51 (t, J=8.33 Hz, 1 H) 6.80 (d, J=8.33 Hz, 1 H) 6.96 (dd, J=8.71, 2.65 Hz, 1 H) 7.05 (td, J=9.28, 2.65 Hz, 1 H) 7.26 - 7.39 (m, 2 H) 7.47 (dd, J=8.90, 3.98 Hz, 1 H) 7.95 (d, J=2.27 Hz, 1 H) 12.26 (br s, 1 H).

[0966]

Example A59

3-{[(5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoic acid

[0967]



[0968]

(1) methyl 5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridine-2-carboxylate

To a mixture of 2-[chloro(cyclohexyl)methyl]-3-methyl-1-benzothiophene (664 mg) synthesized in Example A10(2), methyl 5-aminopyridine-2-carboxylate (362 mg), sodium iodide (714 mg) and N,N-dimethylformamide (10 mL) was added sodium carbonate (505 mg), and the mixture was stirred at 80°C overnight. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (460 mg, 49%) as a pale-yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 - 1.37 (m, 5 H), 1.54 - 1.88 (m, 5 H), 2.07 - 2.18 (m, 1 H), 2.47 (s, 3 H), 3.88 (s, 3 H), 4.54 - 4.68 (m, 2 H), 6.78 (dd, J=8.6, 2.7 Hz, 1 H), 7.22 - 7.30 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.63 (d, J=8.0 Hz, 1 H), 7.68 (d, J=8.0 Hz, 1 H), 7.84 (d, J=8.6 Hz, 1 H), 8.05 (d, J=2.7 Hz, 1 H).

[0969]

(2) 5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridine-2-carboxylic acid

To a mixture of methyl 5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridine-2-carboxylate (460 mg) synthesized above, ethanol (5 mL) and tetrahydrofuran (5 mL) was added 1N aqueous sodium hydroxide solution (5.00 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), 1N hydrochloric acid (5.00 mL) was added at 0°C, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (452 mg, quantitative) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 - 1.38 (m, 5 H), 1.56 - 1.90 (m, 5 H), 2.08 - 2.18 (m, 1 H), 2.50 (s, 3 H), 4.56 - 4.64 (m, 1 H), 4.68 - 4.77 (m, 1 H), 6.88 (dd, J=8.7, 2.6 Hz, 1 H), 7.25 - 7.33 (m, 1 H), 7.34 - 7.41 (m, 1 H), 7.66 (d, J=7.4 Hz, 1 H), 7.71 (d, J=7.7 Hz, 1 H), 7.86 - 7.93 (m, 2 H).

[0970]

(3) ethyl 3-{[(5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoate

To a mixture of 5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridine-2-carboxylic acid (200 mg) synthesized above, ethyl 3-(methylamino)propanoate (104 mg), 1-hydroxybenzotriazole monohydrate (121 mg), triethylamine (220 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (151 mg), and the mixture was stirred at room temperature for 4 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column

chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (141 mg, 54%) as a white solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 - 1.35 (m, 8 H), 1.55 - 1.88 (m, 5 H), 2.06 - 2.17 (m, 1 H), 2.46 (s, 3 H), 2.61 - 2.76 (m, 2 H), 2.98 - 3.18 (m, 3 H), 3.69 - 3.87 (m, 2 H), 3.98 - 4.18 (m, 2 H), 4.39 (d, J=6.0 Hz, 1 H), 4.51 - 4.58 (m, 1 H), 6.81 (dd, J=8.5, 2.7 Hz, 1 H), 7.23 - 7.30 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.39 - 7.55 (m, 1 H), 7.63 (d, J=7.4 Hz, 1 H), 7.70 (d, J=7.7 Hz, 1 H), 7.84 - 7.91 (m, 1 H).

[0971]

(4) 3-{[(5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoic acid

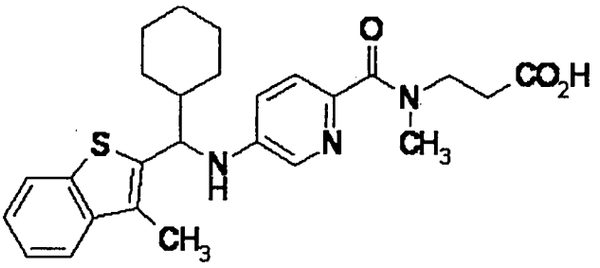
To a mixture of ethyl 3-{[(5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoate (141 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 30 min and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (112 mg, 84%) as a white solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.01 - 1.37 (m, 5 H), 1.54 - 1.89 (m, 5 H), 2.06 - 2.18 (m, 1 H), 2.47 (s, 3 H), 2.73 - 2.90 (m, 2 H), 3.08 (br s, 3 H), 3.76 (t, J=6.4 Hz, 2 H), 4.55 (d, J=8.0 Hz, 1 H), 6.83 - 6.93 (m, 1 H), 7.23 - 7.33 (m, 1 H), 7.33 - 7.41 (m, 1 H), 7.47 - 7.63 (m, 1 H), 7.65 (d, J=7.6 Hz, 1 H), 7.71 (d, J=7.6 Hz, 1 H), 7.85 - 7.94 (m, 1 H).

[0972]

Example A60

3-{[(5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoic acid

[0973]



[0974]

Ethyl 3-{[(5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoate (9.31 g) synthesized in Example A59(3) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/2-propanol (700/300-200/800), flow rate: 60 mL/min-50 mL/min, column temperature: room temperature). The fraction containing an optically active form having a shorter retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (4.67 g, 99.9% ee). To a mixture of the obtained amorphous form, ethanol (20 mL) and tetrahydrofuran (20 mL) was added 1N lithium hydroxide aqueous solution (20 mL), and the mixture was stirred at room temperature for 1 hr and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (20 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (4.17 g, 99%, 99.9% ee) as a white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 1.00 - 1.32 (m, 5 H) 1.37 - 1.51 (m, 1 H) 1.52 - 1.84 (m, 4 H) 2.07 - 2.20 (m, 1 H) 2.46 (s, 3 H) 2.50 - 2.57 (m, 2 H) 2.87 - 3.01 (m, 3 H) 3.27 - 3.36 (m, 5 H) 3.43 - 3.68 (m, 2 H) 4.63 (t, J=7.38 Hz, 1 H) 6.87 (d, J=6.82 Hz, 2 H) 7.19 - 7.41 (m, 3 H) 7.69 (d, J=7.19 Hz, 1 H) 7.79 (d, J=7.57 Hz, 1 H) 7.89 (d, J=2.65 Hz, 1 H) 12.16 (brs, 1 H).

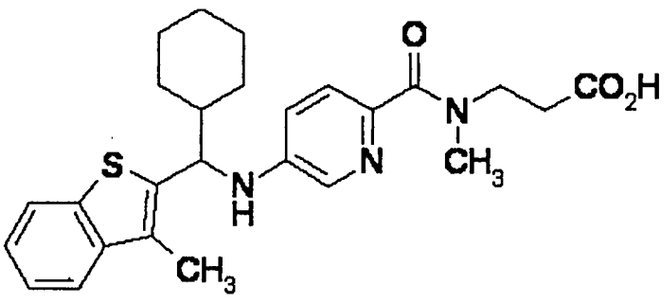
[0975]

413

Example A61

3-{[(5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoic acid

[0976]



[0977]

Ethyl 3-{[(5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridin-2-yl)carbonyl](methyl)amino}propanoate (9.31 g) synthesized in Example A59(3) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/2-propanol (700/300-200/800), flow rate: 60 mL/min-50 mL/min, column temperature: room temperature). The fraction containing an optically active form having a longer retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (4.52 g, 99.9% ee). To a mixture of the obtained amorphous form, ethanol (20 mL) and tetrahydrofuran (20 mL) was added 1N lithium hydroxide aqueous solution (20 mL), and the mixture was stirred at room temperature for 1 hr and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (20 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (4.12 g, 98%, 99.9% ee) as a white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 1.00 - 1.32 (m, 5 H) 1.37 - 1.51 (m, 1 H) 1.52 - 1.84 (m, 4 H) 2.07 - 2.20 (m, 1 H) 2.46

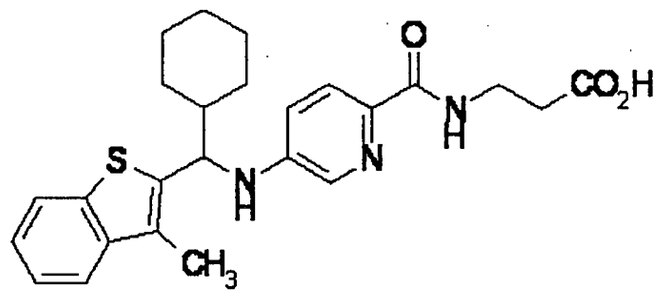
(s, 3 H) 2.50 - 2.57 (m, 2 H) 2.87 - 3.01 (m, 3 H) 3.27 - 3.36 (m, 5 H) 3.43 - 3.68 (m, 2 H) 4.63 (t, J=7.38 Hz, 1 H) 6.87 (d, J=6.82 Hz, 2 H) 7.19 - 7.41 (m, 3 H) 7.69 (d, J=7.19 Hz, 1 H) 7.79 (d, J=7.57 Hz, 1 H) 7.89 (d, J=2.65 Hz, 1 H) 12.16 (brs, 1 H).

[0978]

Example A62

3-{[(5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridin-2-yl)carbonyl]amino}propanoic acid

[0979]



[0980]

(1) ethyl 3-{[(5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridin-2-yl)carbonyl]amino}propanoate

To a mixture of 5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridine-2-carboxylic acid (247 mg) synthesized in Example A59(2), β-alanine ethyl ester hydrochloride (149 mg), 1-hydroxybenzotriazole monohydrate (149 mg), triethylamine (270 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (186 mg), and the mixture was stirred at room temperature overnight. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (274 mg, 88%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.35 (m, 8 H), 1.54 - 1.88 (m, 5 H), 2.06 - 2.18 (m, 1 H), 2.47 (s, 3 H), 2.58 (t, J=6.3 Hz, 2 H), 3.61 - 3.71 (m, 2 H), 4.13 (q, J=7.1 Hz, 2 H), 4.48 - 4.60 (m, 2 H), 6.80 - 6.87 (m, 1 H), 7.22 - 7.30 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.64 (d, J=7.4 Hz, 1 H), 7.69 (d, J=8.0 Hz, 1 H), 7.83 - 7.88 (m, 2 H), 8.07 (t, J=6.3 Hz, 1 H).

[0981]

(2) 3-{[(5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridin-2-yl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(5-{[cyclohexyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}pyridin-2-yl)carbonyl]amino}propanoate (274 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (235 mg, 91%) as a white solid.

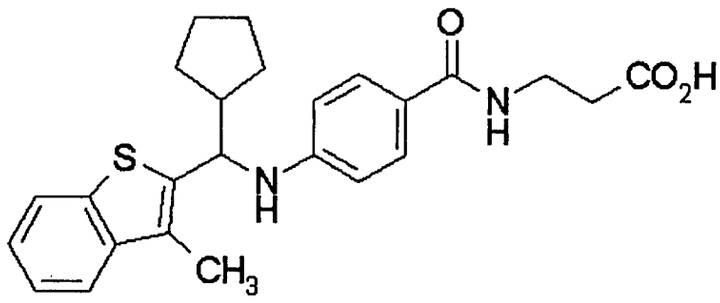
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.36 (m, 5 H), 1.54 - 1.89 (m, 5 H), 2.06 - 2.18 (m, 1 H), 2.47 (s, 3 H), 2.64 (t, J=6.0 Hz, 2 H), 3.61 - 3.73 (m, 2 H), 4.56 (d, J=7.9 Hz, 1 H), 6.84 (dd, J=8.5, 2.4 Hz, 1 H), 7.22 - 7.31 (m, 1 H), 7.31 - 7.40 (m, 1 H), 7.64 (d, J=7.9 Hz, 1 H), 7.69 (d, J=7.9 Hz, 1 H), 7.82 - 7.91 (m, 2 H), 8.11 (t, J=6.0 Hz, 1 H).

[0982]

Example A63

3-{[(4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[0983]



[0984]

(1) cyclopentyl(3-methyl-1-benzothiophen-2-yl)methanone

To a mixture of 3-methyl-1-benzothiophene (1.00 g), cyclopentanecarbonyl chloride (903 μL) and nitromethane (10 mL) was added aluminum chloride (1.35 g) at 0°C, and the mixture was stirred for 1.5 hr. Water was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by NH-silica gel column chromatography (ethyl acetate) to give the title object compound (1.54 g, 93%) as a pale-brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.60 - 1.84 (m, 4 H), 1.92 - 2.03 (m, 4 H), 2.78 (s, 3 H), 3.48 - 3.60 (m, 1 H), 7.40 - 7.52 (m, 2 H), 7.81 - 7.91 (m, 2 H).

[0985]

(2) methyl 4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}benzoate

To a mixture of cyclopentyl(3-methyl-1-benzothiophen-2-yl)methanone (1.54 g) synthesized above, methyl 4-aminobenzoate (1.05 g), triethylamine (7.02 mL) and methylene chloride (30 mL) was added titanium (IV) chloride (829 μL), and the mixture was stirred under argon atmosphere at room temperature for 3 days. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, methylene chloride was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and

concentrated under reduced pressure to give a dark brown oil. To a solution (30 mL) of the obtained oil in tetrahydrofuran were added acetic acid (721 μL) and sodium cyanoborohydride (792 mg), and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, the organic solvent was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 30% ethyl acetate/hexane) to give the title object compound (1.56 g, 65%) as an orange solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 - 1.44 (m, 1 H), 1.45 - 1.82 (m, 6 H), 1.90 - 2.06 (m, 1 H), 2.28 - 2.46 (m, 1 H), 2.50 (s, 3 H), 3.79 (s, 3 H), 4.47 - 4.56 (m, 1 H), 4.62 (d, J=9.1 Hz, 1 H), 6.51 (d, J=9.1 Hz, 2 H), 7.22 - 7.29 (m, 1 H), 7.31 - 7.37 (m, 1 H), 7.61 - 7.66 (m, 1 H), 7.67 - 7.72 (m, 1 H), 7.76 (d, J=9.1 Hz, 2 H).

[0986]

(3) 4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}benzoic acid

[0987]

To a mixture of methyl 4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}benzoate (1.56 g) synthesized above, tetrahydrofuran (20 mL) and ethanol (20 mL) was added 1N aqueous sodium hydroxide solution (20.0 mL), and the mixture was stirred with heating under reflux for 4 hr, and concentrated under reduced pressure. The residue was dissolved in water (40 mL), and 1N hydrochloric acid (20.0 mL) was added at 0°C. The resulting precipitate was collected by filtration, and the obtained pale-brown solid was dissolved in ethyl acetate. The solution was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (1.42 g, 95%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 - 1.45 (m, 1 H), 1.45 - 1.82 (m, 6 H), 1.90 - 2.05 (m, 1 H), 2.27 - 2.45 (m, 1 H), 2.50 (s, 3 H), 4.63 (d, J=9.1 Hz, 1 H), 6.52 (d, J=8.8 Hz, 2 H), 7.22 - 7.29 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.61 - 7.66 (m, 1 H), 7.67 - 7.71 (m, 1 H), 7.80 (d, J=8.8 Hz, 2 H).

[0988]

(4) ethyl 3-{[(4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}benzoic acid (300 mg) synthesized above, β-alanine ethyl ester hydrochloride (189 mg), 1-hydroxybenzotriazole monohydrate (188 mg), triethylamine (343 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (236 mg), and the mixture was stirred at room temperature for 5 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (331 mg, 87%) as a pale-brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.23 (t, J=7.1 Hz, 3 H), 1.30 - 1.45 (m, 1 H), 1.45 - 1.81 (m, 6 H), 1.90 - 2.07 (m, 1 H), 2.27 - 2.47 (m, 1 H), 2.50 (s, 3 H), 2.56 (t, J=5.8 Hz, 2 H), 3.59 - 3.68 (m, 2 H), 4.12 (q, J=7.1 Hz, 2 H), 4.42 (d, J=5.7 Hz, 1 H), 4.60 (dd, J=9.1, 5.7 Hz, 1 H), 6.48 - 6.60 (m, 3 H), 7.21 - 7.29 (m, 1 H), 7.30 - 7.37 (m, 1 H), 7.50 (d, J=8.8 Hz, 2 H), 7.61 - 7.65 (m, 1 H), 7.66 - 7.72 (m, 1 H).

[0989]

(5) 3-{[(4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclopentyl(3-methyl-1-benzothiophen-2-

yl)methyl]amino}phenyl)carbonyl]amino}propanoate (331 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 1.5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (276 mg, 89%) as a white solid.

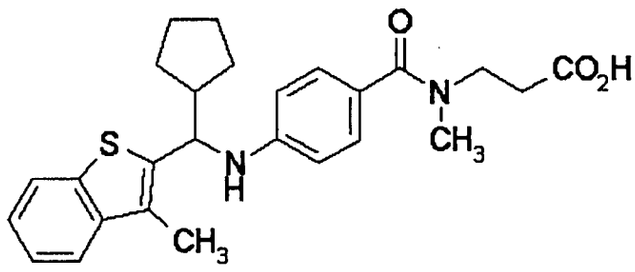
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.28 - 1.43 (m, 1 H), 1.44 - 1.80 (m, 6 H), 1.89 - 2.03 (m, 1 H), 2.25 - 2.43 (m, 1 H), 2.48 (s, 3 H), 2.56 (t, J=5.3 Hz, 2 H), 3.52 - 3.63 (m, 2 H), 4.58 (d, J=9.0 Hz, 1 H), 6.45 - 6.60 (m, 3 H), 7.20 - 7.28 (m, 1 H), 7.29 - 7.37 (m, 1 H), 7.46 (d, J=8.3 Hz, 2 H), 7.62 (d, J=7.5 Hz, 1 H), 7.68 (d, J=7.9 Hz, 1 H).

[0990]

Example A64

3-{[(4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0991]




[0992]

(1) ethyl 3-{[(4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}benzoic acid (300 mg) synthesized in Example A63(3), ethyl 3-(methylamino)propanoate (161 mg), 1-hydroxybenzotriazole monohydrate (188 mg), triethylamine (343 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide hydrochloride (236 mg), and the mixture was stirred at room temperature for 5 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (228 mg, 58%) as a pale-brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.21 (t, J=7.2 Hz, 3 H), 1.31 - 1.44 (m, 1 H), 1.45 - 1.83 (m, 6 H), 1.89 - 2.04 (m, 1 H), 2.28 - 2.43 (m, 1 H), 2.49 (s, 3 H), 2.59 (t, J=7.1 Hz, 2 H), 2.98 (s, 3 H), 3.68 (t, J=7.1 Hz, 2 H), 4.09 (q, J=7.2 Hz, 2 H), 4.27 - 4.33 (m, 1 H), 4.53 - 4.61 (m, 1 H), 6.51 (d, J=8.5 Hz, 2 H), 7.17 (d, J=8.5 Hz, 2 H), 7.22 - 7.29 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.61 - 7.66 (m, 1 H), 7.68 - 7.73 (m, 1 H).

[0993]

(2) 3-{[(4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (228 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 3 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (198 mg, 92%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.28 - 1.44 (m, 1 H), 1.44 - 1.79 (m, 6 H), 1.89 - 2.04 (m, 1 H), 2.26 - 2.43 (m, 1 H), 2.49 (s, 3 H), 2.62 (t, J=6.2 Hz, 2 H), 2.98 (s, 3 H), 3.66 (t, J=6.2 Hz, 2 H), 4.57 (d, J=9.0 Hz, 1 H), 6.51 (d, J=8.5 Hz, 2 H),

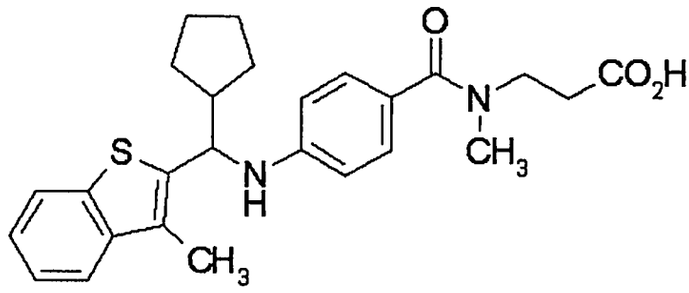
7.20 (d, J=8.5 Hz, 2 H), 7.23 - 7.30 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.64 (d, J=7.5 Hz, 1 H), 7.71 (d, J=7.5 Hz, 1 H).

[0994]

Example A65

3-{[(4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0995]



[0996]

Ethyl 3-{[(4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (19.7 g) synthesized in Example A64(1) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/ethanol (500/500), flow rate: 60 mL/min, column temperature: room temperature). The fraction containing an optically active form having a shorter retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (8.75 g, 99.9% ee). To a mixture of the obtained amorphous form, ethanol (100 mL) and tetrahydrofuran (100 mL) was added 1N aqueous sodium hydroxide solution (30 mL), and the mixture was stirred at room temperature for 5 hr and concentrated under reduced pressure. The residue was dissolved in water (200 mL), and 1N hydrochloric acid (30 mL) was added at 0°C, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (7.54 g, 41%,99.9% ee) as a white solid. The obtained

solid was recrystallized from ethanol/water to give colorless crystals.

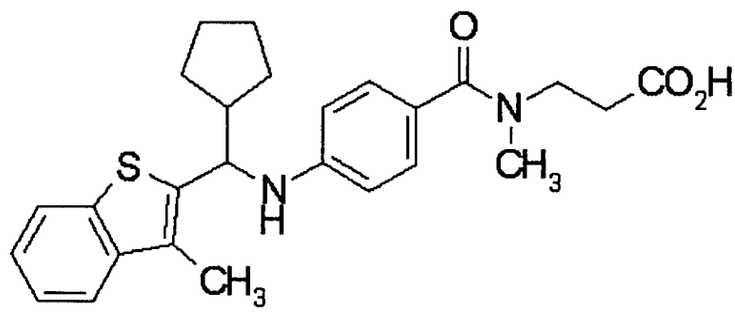
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.28 - 1.44 (m, 1 H), 1.44 - 1.79 (m, 6 H), 1.89 - 2.04 (m, 1 H), 2.26 - 2.43 (m, 1 H), 2.49 (s, 3 H), 2.62 (t, J=6.2 Hz, 2 H), 2.98 (s, 3 H), 3.66 (t, J=6.2 Hz, 2 H), 4.57 (d, J=9.0 Hz, 1 H), 6.51 (d, J=8.5 Hz, 2 H), 7.20 (d, J=8.5 Hz, 2 H), 7.23 - 7.30 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.64 (d, J=7.5 Hz, 1 H), 7.71 (d, J=7.5 Hz, 1 H).

[0997]

Example A66

3-{[(4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[0998]



[0999]

Ethyl 3-{[(4-{[cyclopentyl(3-methyl-1-benzothiophen-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (19.7 g) synthesized in Example A64(1) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/ethanol (500/500), flow rate: 60 mL/min, column temperature: room temperature). The fraction containing an optically active form having a longer retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give an amorphous form (8.95 g, 99.9% ee). To a mixture of the obtained amorphous form, ethanol (100 mL) and tetrahydrofuran (100 mL) was added 1N aqueous sodium hydroxide solution (30 mL), and the mixture was

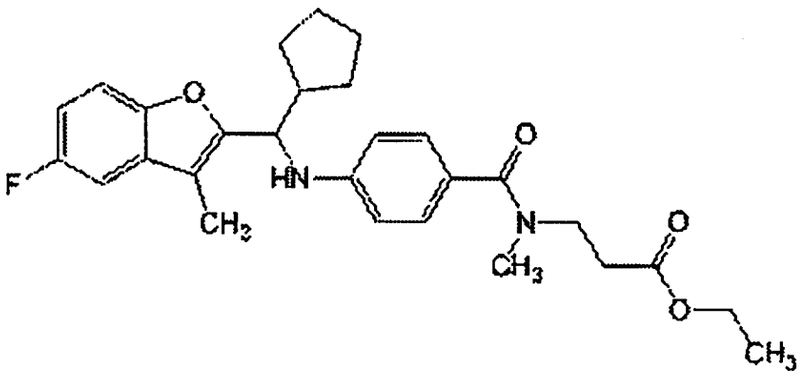
stirred at room temperature for 3 hr and concentrated under reduced pressure. The residue was dissolved in water (200 mL), and 1N hydrochloric acid (35 mL) was added at 0°C, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (8.06 g, 43%, 99.9% ee) as a white solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.28 - 1.44 (m, 1 H), 1.44 - 1.79 (m, 6 H), 1.89 - 2.04 (m, 1 H), 2.26 - 2.43 (m, 1 H), 2.49 (s, 3 H), 2.62 (t, J=6.2 Hz, 2 H), 2.98 (s, 3 H), 3.66 (t, J=6.2 Hz, 2 H), 4.57 (d, J=9.0 Hz, 1 H), 6.51 (d, J=8.5 Hz, 2 H), 7.20 (d, J=8.5 Hz, 2 H), 7.23 - 7.30 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.64 (d, J=7.5 Hz, 1 H), 7.71 (d, J=7.5 Hz, 1 H).

[1000]

Example A67

Ethyl 3-{[(4-{[cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

[1001]




[1002]

(1) (2-acetyl-4-fluorophenoxy)acetic acid

A solution of 5'-fluoro-2'-hydroxyacetophenone (25.0 g), methyl bromoacetate (27.2 g), potassium carbonate (33.6 g) in N,N-dimethylformamide (250 mL) was stirred at room temperature for 1.5 hr. The insoluble material was filtered off, 1N hydrochloric acid was added to the filtrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and

concentrated under reduced pressure to give a brown oil. Tetrahydrofuran (300 mL), ethanol (300 mL) and 1N aqueous sodium hydroxide solution (300 mL) were added to the obtained oil, and the mixture was stirred at room temperature for 30 min. The solvent was concentrated under reduced pressure, 1N hydrochloric acid (300 mL) was added, and the resulting crystals were collected by filtration. The crystals were dissolved in ethyl acetate, dried over magnesium sulfate, and concentrated under reduced pressure to give the title compound (23.7 g, 69%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.68 (s, 3 H), 4.75 (s, 2 H), 6.86 - 7.03 (m, 1 H), 7.13 - 7.30 (m, 1 H), 7.43 - 7.60 (m, 1 H).

[1003]

(2) 5-fluoro-3-methyl-1-benzofuran

A mixture of (2-acetyl-4-fluorophenoxy)acetic acid (22.94 g) synthesized above, sodium acetate (44.38 g) and acetic anhydride (200 mL) was stirred at 110°C for 15 hr. The reaction mixture was cooled to room temperature, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (NH silica, hexane) to give the title compound (14.73 g, 91%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.20 (s, 3 H), 6.91 - 7.03 (m, 1 H), 7.15 (dd, J=8.3, 2.7 Hz, 1 H), 7.35 (dd, J=8.7, 4.2 Hz, 1 H), 7.42 (s, 1 H).

[1004]

(3) cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methanone

To a solution of 5-fluoro-3-methyl-1-benzofuran (2.0 g) synthesized above, cyclopentanecarbonylchloride (1.94 g) in nitromethane (40 mL) was added aluminum chloride (anhydrous) (2.66 g) at 0°C, and the mixture was stirred for 3 hr. Water

was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 95:5, v/v) to give the title compound (2.11 g, 64%) as a colorless amorphous form.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.67 - 2.09 (m, 8 H), 2.57 (s, 3 H), 3.64 - 3.91 (m, 1 H), 7.10 - 7.23 (m, 1 H), 7.25 - 7.31 (m, 1 H), 7.38 - 7.53 (m, 1 H).

[1005]

(4) cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methanol

Cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methanone (27.15 g) synthesized above was dissolved in a mixed solvent of methanol (40 mL)-tetrahydrofuran (240 mL), and sodium tetrahydroborate (90%, 5.5 g) was added at 0°C. The reaction mixture was stirred at 0°C for 2 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give the title compound (29.26 g, 100%) as a yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 - 1.20 (m, 1 H), 1.42 - 1.77 (m, 6 H), 1.92 - 2.02 (m, 2 H), 2.21 (s, 3 H), 2.42 - 2.60 (m, 1 H), 4.56 (dd, J=9.3, 5.9 Hz, 1 H), 6.97 (td, J=9.1, 2.7 Hz, 1 H), 7.11 (dd, J=8.7, 2.7 Hz, 1 H), 7.33 (dd, J=8.9, 4.0 Hz, 1 H).

[1006]

(5) ethyl 3-{[(4-{[cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a solution of cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methanol (27.31 g) obtained above in tetrahydrofuran (200 mL) was added thionyl chloride (12.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 hr. To the reaction mixture was added

aqueous sodium hydrogen carbonate solution ice-cooled to 0°C, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated, ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (28.90 g) obtained in Example 2(2), sodium iodide (16.48 g), sodium carbonate (23.3 g) and N,N-dimethylacetamide (200 mL) were added to the obtained residue, and the mixture was stirred at 80°C for 18 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 50:50, v/v) to give the title compound (17.88 g, 34%) as a yellow amorphous.

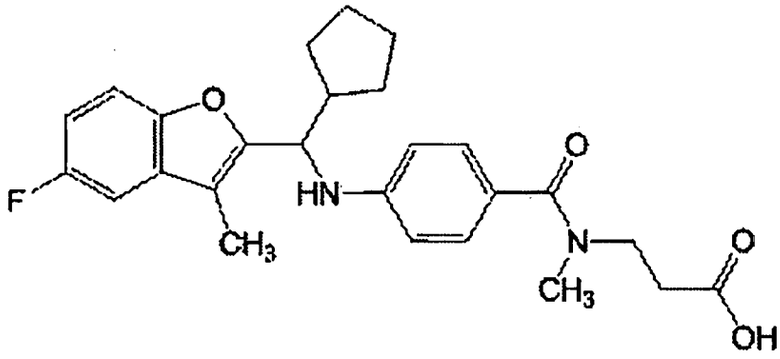
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.21 - 1.31 (m, 3 H), 1.50 - 1.70 (m, 8 H), 1.92 - 2.01 (m, 1 H), 2.25 (s, 3 H), 2.42 - 2.55 (m, 1 H), 2.58 (t, J=5.9 Hz, 2 H), 3.65 (q, J=6.1 Hz, 2 H), 4.31 - 4.49 (m, 2 H), 6.57 (d, J=8.7 Hz, 3 H), 6.84 - 6.98 (m, 1 H), 7.06 (dd, J=8.3, 2.7 Hz, 1 H), 7.21 - 7.32 (m, 1 H), 7.54 (d, J=8.7 Hz, 2 H).

[1007]

Example A68

3-{[(4-{[cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1008]




[1009]

Ethyl 3-{[(4-{[cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (460 mg) obtained in Example A67(5) was dissolved in ethanol (1.9 mL) and tetrahydrofuran (1.9 mL), 1N aqueous sodium hydroxide solution (1.9 mL) was added, and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure. Water (6 mL) was added, and the mixture was neutralized with 1N hydrochloric acid under ice-cooling and stirred for 1 hr. The resulting precipitate was collected by filtration and dried to give the title compound (352 mg, 81%) as a colorless solid.

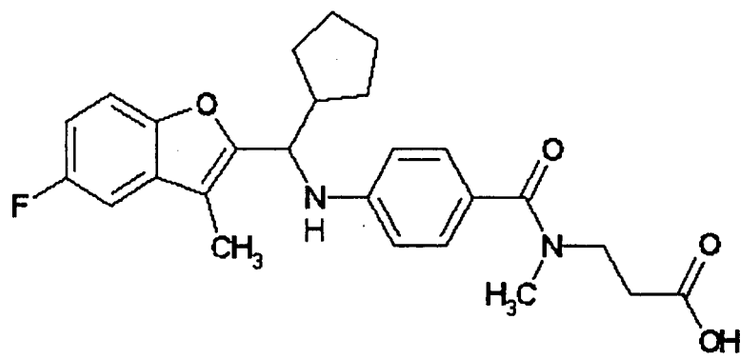
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.23 - 1.74 (m, 8 H), 1.90 - 2.08 (m, 1 H), 2.24 (s, 3 H), 2.47 (d, J=8.0 Hz, 1 H), 2.60 - 2.70 (m, 2 H), 3.01 (s, 3 H), 3.69 (t, J=6.6 Hz, 2 H), 4.36 (d, J=9.1 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.86 - 6.97 (m, 1 H), 7.07 (dd, J=8.7, 2.7 Hz, 1 H), 7.18 - 7.31 (m, 3 H).

[1010]

Example A69

3-{[(4-{[cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1011]




[1012]

Ethyl 3-{[(4-{[cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (4.18 g) obtained in Example A67(5) was dissolved in hexane-ethanol

(1:1, volume ratio), subjected to HPLC using CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd.), and eluted with hexane-ethanol (1:1, volume ratio) as a mobile phase at 30°C and at a flow rate 60 mL/min. The resulting fraction containing an optically active form having a shorter retention time was concentrated to give an amorphous form (2.07 g, 99.9% ee). The obtained amorphous form was dissolved in ethanol (9 mL) and tetrahydrofuran (9 mL), 1N aqueous sodium hydroxide solution (8.6 mL) was added, and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure, water (15 mL) was added, and the mixture was under ice-cooling neutralized with 1N hydrochloric acid (8.6 mL), and stirred for 1 hr. The resulting precipitate was collected by filtration, and dried to give the title compound (1.81 g, 93%, 99.9% ee) as a colorless amorphous form. The obtained colorless amorphous (150 mg) was crystallized from 2-propanol/water to give colorless 2-propanol-containing crystals (140 mg). In addition, the colorless amorphous (773 mg) obtained above was crystallized from ethanol/water to give ethanol-containing crystals (756 mg). The ethanol-containing crystals (756 mg) were recrystallized from diethyl ether to give colorless crystals (553 mg) free of solvent.

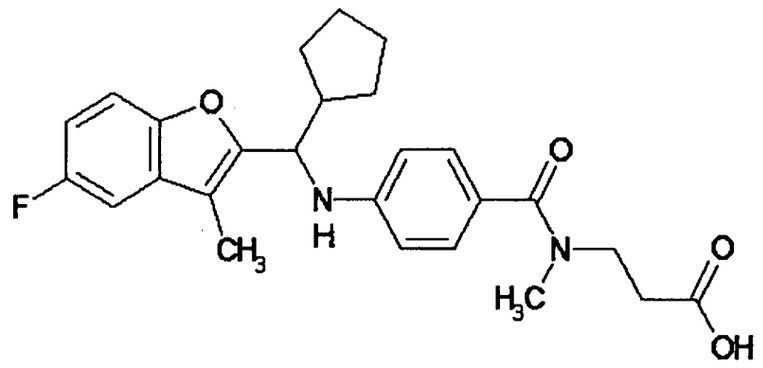
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.15 - 1.72 (m, 7 H), 1.86 - 2.09 (m, 1 H), 2.24 (s, 3 H), 2.40 - 2.53 (m, 1 H), 2.62 (t, J=6.2 Hz, 2 H), 3.00 (s, 3 H), 3.68 (t, J=6.6 Hz, 2 H), 4.36 (d, J=9.0 Hz, 1 H), 6.54 (d, J=8.7 Hz, 2 H), 6.91 (td, J=8.9, 2.6 Hz, 1 H), 7.06 (dd, J=8.7, 2.6 Hz, 1 H), 7.19 - 7.30 (m, 3 H).

[1013]

Example A70

3-{[(4-{[cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1014]



[1015]

Ethyl 3-{[(4-{[cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (4.18 g) obtained in Example A67(5) was dissolved in hexane-ethanol (1:1, volume ratio), subjected to HPLC using CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd.), and eluted with hexane-ethanol (1:1, volume ratio) as a mobile phase at 30°C and at a flow rate 60 mL/min. The resulting fraction containing an optically active form having a longer retention time was concentrated to give an amorphous form (2.04 g, 99.9% ee). The obtained amorphous form (2.04 g) was dissolved in ethanol (9 mL) and tetrahydrofuran (9 mL), 1N aqueous sodium hydroxide solution (8.5 mL) was added, and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure, water (15 mL) was added, and the mixture was neutralized with 1N hydrochloric acid (8.5 mL) under ice-cooling, and stirred for 1 hr. The resulting precipitate was collected by filtration, and dried to give the title compound (1.88 g, 98%, 99.9% ee) as a colorless amorphous form.

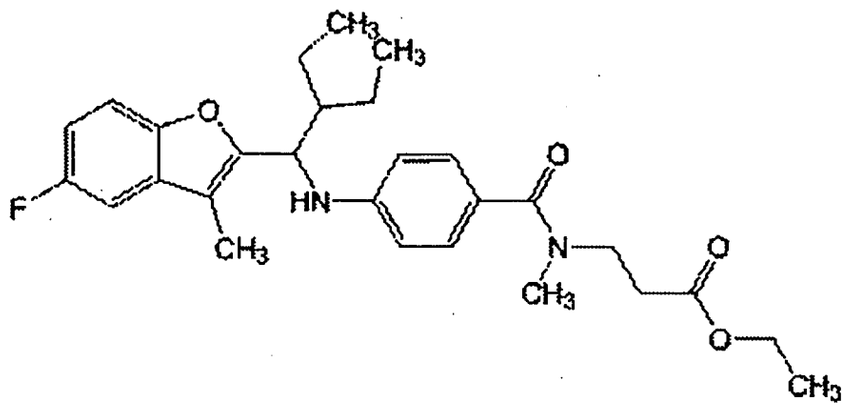
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.23 - 1.75 (m, 7 H), 1.86 - 2.03 (m, 1 H), 2.25 (s, 3 H), 2.39 - 2.54 (m, 1 H), 2.63 (t, J=6.4 Hz, 2 H), 3.01 (s, 3 H), 3.69 (t, J=6.6 Hz, 2 H), 4.36 (d, J=9.1 Hz, 1 H), 4.48 (br. s., 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.92 (td, J=8.9, 2.7 Hz, 1 H), 7.07 (dd, J=8.5, 2.5 Hz, 1 H), 7.16 - 7.32 (m, 3 H).

[1016]

Example A71

ethyl 3-{[(4-{[2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoate

[1017]



[1018]

(1) 2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butan-1-one

To a solution of 5-fluoro-3-methyl-1-benzofuran (12.0 g) synthesized in Example A67(2), 2-ethylbutyrylchloride (9.58 g) in nitromethane (240 mL) was added aluminum chloride (anhydrous) (12.94 g) at 0°C, and the mixture was stirred for 1.5 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 90:10, v/v) to give the title compound (15.02 g, 93%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (t, J=7.6 Hz, 6 H), 1.59 - 1.67 (m, 2 H), 1.75 - 1.91 (m, 2 H), 2.58 (s, 3 H), 3.26 - 3.42 (m, 1 H), 7.11 - 7.35 (m, 2 H), 7.40 - 7.55 (m, 1 H).

[1019]

(2) 2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butan-1-ol

2-Ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butan-1-one (15.0 g) synthesized above was dissolved in a mixed solvent of methanol (50 mL)-tetrahydrofuran (250 mL), and sodium tetrahydroborate (90%, 5.1 g) was added at 0°C. The

reaction mixture was stirred at 0°C for 1.5 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give the title compound (16.17 g, 100%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.75 - 0.86 (m, 3 H), 0.95 (t, J=7.6 Hz, 3 H), 1.10 - 1.35 (m, 2 H), 1.66 - 1.94 (m, 3 H), 2.21 (s, 3 H), 4.66 - 4.81 (m, 1 H), 6.90 - 7.02 (m, 1 H), 7.11 (dd, J=8.7, 2.7 Hz, 1 H), 7.30 - 7.40 (m, 1 H).

[1020]

(3) methyl 4-{[2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}benzoate

To a solution of 2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butan-1-ol (1.00 g) synthesized above in tetrahydrofuran (10 mL) was added thionyl chloride (320 μL), and the mixture was stirred at room temperature for 3.5 hr. The reaction mixture was poured into ice-cooled saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a yellow oil (1.11 g). A solution of this yellow oil (1.11 g), methyl 4-aminobenzoate (638 mg), sodium iodide (1.20 g) and sodium carbonate (852 mg) in N,N-dimethylformamide (10 mL) was stirred at 100°C for 20 hr. Water was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 90:10, v/v) to give the title compound (790 mg, 52%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 (t, J=7.5 Hz, 6 H), 1.62 - 1.73 (m, 2 H), 1.84 - 1.94 (m, 2 H), 2.23 (s, 3 H), 3.81 (s, 3 H), 4.46 - 4.52 (m, 1 H), 4.56 - 4.65 (m, 1 H), 4.68 - 4.76 (m,

1 H), 6.54 - 6.61 (m, 2 H), 6.85 - 7.00 (m, 1 H), 7.04 - 7.15 (m, 1 H), 7.29 - 7.37 (m, 1 H), 7.80 (d, J=9.0 Hz, 2 H).

[1021]

(4) 4-{[2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}benzoic acid

To a mixture of methyl 4-{[2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}benzoate (709 mg) synthesized above, tetrahydrofuran (6 mL) and ethanol (6 mL) was added 1N aqueous sodium hydroxide solution (3.7 mL), and the mixture was heated under reflux for 14 hr. 1N Aqueous sodium hydroxide solution (4.0 mL) was added, and the mixture was further stirred with heating under reflux for 2 hr. 8N Aqueous sodium hydroxide solution (2.0 mL) and ethanol (2 mL) were added to the mixture, and the mixture was further stirred with heating under reflux for 1 hr. The reaction mixture was concentrated under reduced pressure, 8N aqueous sodium hydroxide solution (4.0 mL), ethanol (4 mL) and tetrahydrofuran (4 mL) were added, and the mixture was further stirred with heating under reflux for 1 hr. The reaction mixture was allowed to cool to room temperature, 1N hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 100:0 - 70:30, v/v) to give the title compound (412 mg, 61%) as a colorless amorphous form.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.80 - 1.02 (m, 6 H), 1.32 - 1.72 (m, 4 H), 1.83 - 1.97 (m, 1 H), 2.23 (s, 3 H), 4.51 - 4.71 (m, 2 H), 6.57 (d, J=8.7 Hz, 2 H), 6.87 - 6.98 (m, 1 H), 7.07 (dd, J=8.3, 2.7 Hz, 1 H), 7.27 - 7.35 (m, 1 H), 7.86 (d, J=8.7 Hz, 2 H).

[1022]

(5) ethyl 3-{[(4-{[2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoate

A mixture of 4-{[2-ethyl-1-(5-fluoro-3-methyl-1-

benzofuran-2-yl)butyl]amino}benzoic acid (10.77 g) synthesized above, ethyl 3-(methylamino)propanoate (4.59 g), 1-hydroxybenzotriazole·monohydrate (5.34 g), triethylamine (3.53 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (6.69 g) and N,N-dimethylformamide (100 mL) was stirred at room temperature for 14 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 100:0 - 0:100, v/v) to give the title compound (9.83 g, 70%) as a yellow amorphous.

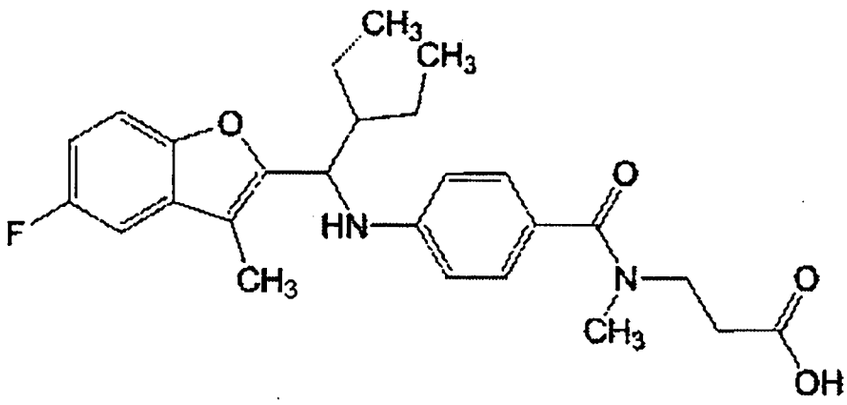
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.80 - 0.88 (m, 3 H), 0.95 (t, J=7.3 Hz, 3 H), 1.19 - 1.25 (m, 5 H), 1.33 - 1.54 (m, 2 H), 1.87 (dt, J=7.3, 4.9 Hz, 1 H), 2.22 (s, 3 H), 2.61 (t, J=7.0 Hz, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.2 Hz, 2 H), 4.11 (q, J=6.9 Hz, 2 H), 4.28 (d, J=8.7 Hz, 1 H), 4.56 (t, J=8.3 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.92 (td, J=9.0, 2.6 Hz, 1 H), 7.06 (dd, J=8.3, 2.6 Hz, 1 H), 7.22 (d, J=8.7 Hz, 2 H), 7.25 - 7.31 (m, 1 H).

[1023]

Example A72

3-{[(4-{[2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1024]




[1025]

To a mixture of ethyl 3-{[(4-{[2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoate (132 mg) obtained in Example A71(5) in tetrahydrofuran (1 mL) and ethanol (1 mL) was added 1N aqueous sodium hydroxide solution (0.54 mL), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in water (4 mL), and 1N hydrochloric acid (0.54 mL) was added at 0°C. The mixture was stirred at 0°C for 1 hr, and the resulting precipitate was collected by filtration to give the title compound (103 mg, 70%) as a colorless amorphous form.

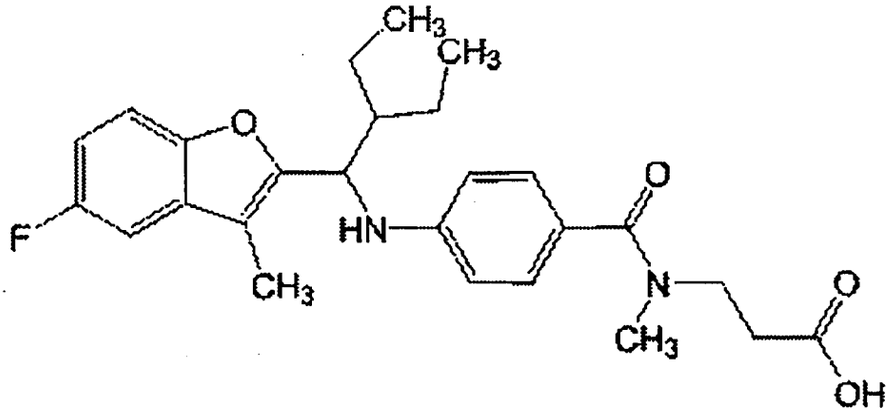
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.79 - 1.01 (m, 6 H), 1.12 - 1.90 (m, 6 H), 2.21 (s, 3 H), 2.58 - 2.69 (m, 2 H), 3.00 (s, 3 H), 3.66 (d, 2 H), 4.56 (d, J=8.0 Hz, 1 H), 6.55 (d, J=8.3 Hz, 2 H), 6.92 (td, J=8.9, 2.7 Hz, 1 H), 7.06 (dd, J=8.3, 2.7 Hz, 1 H), 7.19 - 7.36 (m, 3 H).

[1026]

Example A73

3-{[(4-{[2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1027]




[1028]

Ethyl 3-{[(4-{[2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoate (9.18 g) obtained in Example A71(5) was dissolved in hexane-ethanol (1:1, volume ratio), subjected to HPLC using CHIRALPAK

AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd.), and eluted with hexane-ethanol (1:1, volume ratio) as a mobile phase at room temperature and at a flow rate 60 mL/min. The resulting fraction containing an optically active form having a shorter retention time was concentrated to give an amorphous form (4.56 g, 99.9% ee). The obtained amorphous form (4.56 g) was dissolved in ethanol (19 mL) and tetrahydrofuran (19 mL), 1N aqueous sodium hydroxide solution (18.6 mL) was added, and the mixture was stirred at room temperature for 20 min. The solvent was evaporated under reduced pressure. Water (30 mL) was added, and the mixture was neutralized with 1N hydrochloric acid (18.6 mL) under ice-cooling and stirred for 20 min. The resulting precipitate was collected by filtration, and dried to give the title compound (3.63 g, 86%, 99.9% ee) as a colorless amorphous form. The obtained colorless amorphous (1.0 g) was crystallized from 2-propanol/water to give colorless crystals (927 mg).

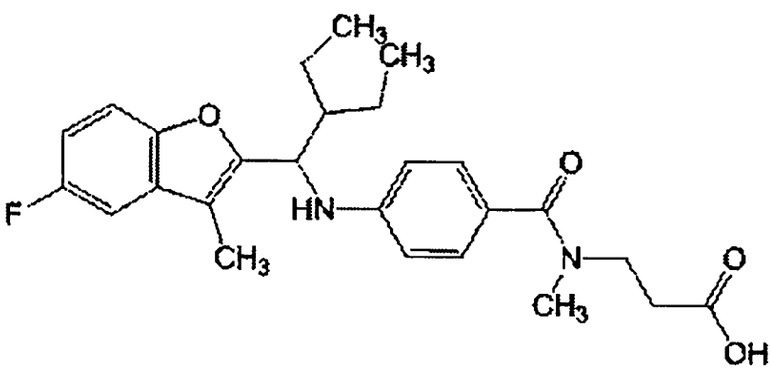
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 (t, J=7.3 Hz, 3 H), 0.94 (t, J=7.5 Hz, 3 H), 1.11 - 1.72 (m, 4 H), 1.77 - 1.92 (m, 1 H), 2.22 (s, 3 H), 2.65 (t, J=6.6 Hz, 2 H), 3.02 (s, 3 H), 3.69 (t, J=6.8 Hz, 2 H), 4.56 (d, J=7.9 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.92 (td, J=9.0, 2.6 Hz, 1 H), 7.06 (dd, J=8.5, 2.4 Hz, 1 H), 7.18 - 7.39 (m, 3 H).

[1029]

Example A74

3-{[(4-{[2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1030]



[1031]

Ethyl 3-{[(4-{[2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoate (9.18 g) obtained in Example A71(5) was dissolved in hexane-ethanol (1:1, volume ratio), subjected to HPLC using CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd.), and eluted with hexane-ethanol (1:1, volume ratio) as a mobile phase at room temperature and at a flow rate 60 mL/min. The resulting fraction containing an optically active form having a longer retention time was concentrated to give an amorphous form (4.67 g, 99.9% ee). The obtained amorphous form (4.67 g) was dissolved in ethanol (20 mL) and tetrahydrofuran (20 mL), 1N aqueous sodium hydroxide solution (19.4 mL) was added, and the mixture was stirred at room temperature for 20 min. The solvent was evaporated under reduced pressure. Water (30 mL) was added, and the mixture was neutralized with 1N hydrochloric acid under ice-cooling and stirred for 20 min. The resulting precipitate was collected by filtration, and dried to give the title compound (4.21 g, 96%, 99.9% ee).

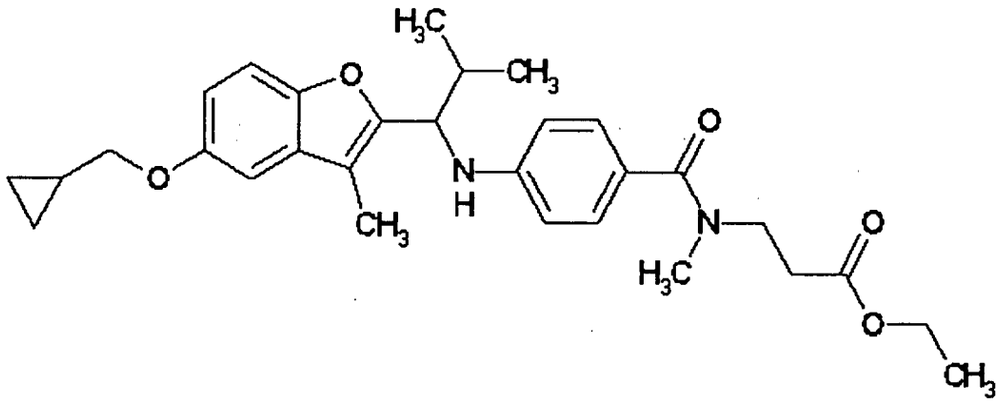
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.80 - 0.89 (m, 3 H), 0.94 (t, J=7.5 Hz, 3 H), 1.16 - 1.71 (m, 4 H), 1.74 - 1.91 (m, 1 H), 2.22 (s, 3 H), 2.62 (t, J=6.2 Hz, 2 H), 3.01 (s, 3 H), 3.61 - 3.76 (m, 2 H), 4.56 (d, J=7.9 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.92 (td, J=9.0, 2.6 Hz, 1 H), 7.06 (dd, J=8.5, 2.4 Hz, 1 H), 7.16 - 7.31 (m, 3 H).

[1032]

Example A75

ethyl 3-[{[4-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

[1033]



[1034]

(1) 1-bromo-3-methylbutan-2-one

To a solution of 3-methyl-2-butanone (43.0 g) in methanol (300 mL) was added dropwise bromine (80 g) over 20 min while cooling in an ice bath. The ice bath was removed, and the mixture was stirred at room temperature for 40 min. Water (450 mL) was added to the reaction mixture, and the mixture was stirred for 20 min. The reaction mixture was extracted twice with diethyl ether (500 mL). The extract was washed with water (400 mL), 10% aqueous potassium carbonate solution (400 mL) and saturated brine (200 mL), dried over magnesium sulfate, and concentrated under reduced pressure to give the title compound (55.9 g) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.17 (d, J=6.8 Hz, 6 H), 2.88 - 3.05 (m, 1 H), 3.98 (s, 2 H).

[1035]

(2) 1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-one

A solution of 2',5'-dihydroxyacetophenone (25.0 g), bromomethylcyclopropane (24.43 g), potassium carbonate (27.2 g) in acetonitrile (400 mL) was stirred with heating under reflux for 2.5 hr. Bromomethylcyclopropane (4.4 g) was added to the mixture, and the mixture was further stirred with heating under reflux for 14 hr. The reaction mixture was cooled to room temperature, the insoluble material was filtered off, and the filtrate was concentrated under reduced

pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 100:0 - 10:90, v/v) to give 1-[5-(cyclopropylmethoxy)-2-hydroxyphenyl]ethanone (35.5 g) as a yellow oil at purity 70%. A solution of the obtained 1-[5-(cyclopropylmethoxy)-2-hydroxyphenyl]ethanone (35.5 g), 1-bromo-3-methylbutan-2-one (35.5 g) synthesized above and potassium carbonate (66.3 g) in N,N-dimethylformamide (350 mL) was stirred at room temperature for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. 1,8-Diazabicyclo[5.4.0]undec-7-ene (22.5 mL) and N,N-dimethylformamide (300 mL) were added to the obtained residue, and the mixture was stirred at 100°C for 30 min. The reaction mixture was cooled to room temperature, 1N hydrochloric acid (300 mL) was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 100:0 - 90:10, v/v) to give the title compound (19.91 g, 45%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.29 - 0.50 (m, 2 H), 0.61 - 0.73 (m, 2 H), 1.01 - 1.46 (m, 7 H), 2.57 (s, 3 H), 3.44 - 3.68 (m, 1 H), 3.86 (d, J=7.2 Hz, 2 H), 7.00 (d, J=2.3 Hz, 1 H), 7.11 (dd, J=9.0, 2.6 Hz, 1 H), 7.39 (d, J=9.0 Hz, 1 H).

[1036]

(3) 1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-ol

1-[5-(Cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-one (19.91 g) synthesized above was dissolved in mixed solvent of methanol (40 mL)-tetrahydrofuran (200 mL), and sodium tetrahydroborate (90%, 5.53 g) was added at 0°C. The reaction mixture was stirred at 0°C for 30 min. Water was added to the reaction mixture and the mixture was extracted

with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give the title compound (22.74 g, 100%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.32 - 0.42 (m, 2 H), 0.60 - 0.71 (m, 2 H), 0.81 (d, 3 H), 1.12 (d, J=6.4 Hz, 3 H), 1.26 - 1.36 (m, 1 H), 1.99 (d, J=6.0 Hz, 1 H), 2.17 - 2.28 (m, 4 H), 3.84 (d, 2 H), 4.45 (dd, J=8.3, 6.4 Hz, 1 H), 6.84 - 6.96 (m, 2 H), 7.29 (d, J=8.7 Hz, 1 H).

[1037]

(4) ethyl 3-[{[4-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

To a solution of 1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-ol (22.74 g) obtained above in tetrahydrofuran (200 mL) was added thionyl chloride (6.4 mL) at room temperature. The reaction mixture was stirred at room temperature for 1.5 hr. To the reaction mixture was added ice-cooled to 0°C aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated, ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (19.2 g) obtained in Example 2(2), sodium iodide (21.9 g), sodium carbonate (15.4 g) and N,N-dimethylacetamide (200 mL) were added to the obtained residue, and the mixture was stirred at 80°C for 1.5 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 50:50, v/v) to give the title compound (18.34 g, 50%) as a yellow amorphous.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.29 - 0.40 (m, 2 H), 0.58 - 0.70

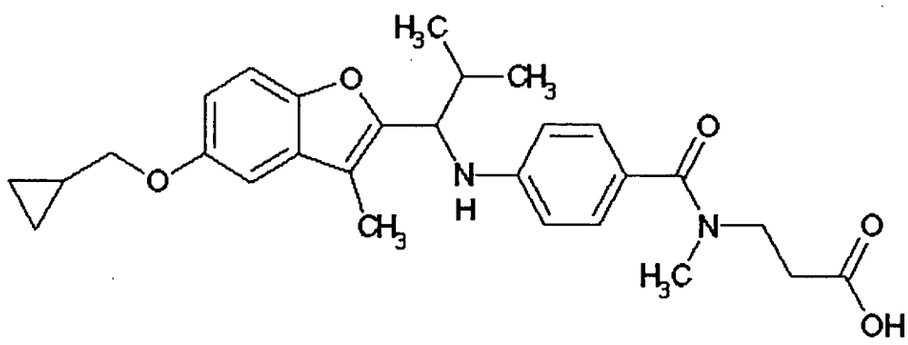
(m, 2 H), 0.91 (d, J=6.8 Hz, 3 H), 1.12 (d, J=6.8 Hz, 3 H), 1.19 - 1.33 (m, 4 H), 2.17 - 2.28 (m, 4 H), 2.61 (t, J=6.8 Hz, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.2 Hz, 2 H), 3.82 (d, J=7.2 Hz, 2 H), 4.05 - 4.16 (m, 2 H), 4.27 - 4.38 (m, 2 H), 6.57 (d, J=9.0 Hz, 2 H), 6.78 - 6.91 (m, 2 H), 7.17 - 7.25 (m, 3 H).

[1038]

Example A76

3-[{[4-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1039]



[1040]

To a mixture of ethyl 3-[{[4-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (667 mg) obtained in Example A75(4) in tetrahydrofuran (3 mL) and ethanol (3 mL) was added 1N aqueous sodium hydroxide solution (2.6 mL), and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in water (4 mL), and 1N hydrochloric acid (2.6 mL) was added at 0°C. The mixture was stirred at 0°C for 30 min, and the resulting precipitate was collected by filtration to give the title compound (509 mg, 81%) as a colorless amorphous form.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.28 - 0.40 (m, 2 H), 0.58 - 0.71 (m, 2 H), 0.91 (d, J=6.8 Hz, 3 H), 1.11 (d, J=6.8 Hz, 3 H), 1.23 - 1.34 (m, 1 H), 2.17 - 2.28 (m, 4 H), 2.64 (t, J=6.4 Hz,

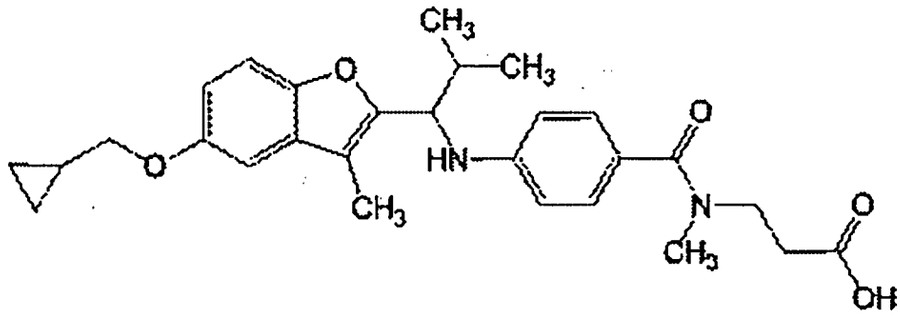
2 H), 3.02 (s, 3 H), 3.69 (t, J=6.4 Hz, 2 H), 3.82 (d, J=7.2 Hz, 2 H), 4.31 (d, J=8.0 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.78 - 6.91 (m, 2 H), 7.19 - 7.25 (m, 3 H).

[1041]

Example A77

3-[{[4-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1042]



[1043]

Ethyl 3-[{[4-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (18.23 g) obtained in Example A75(4) was dissolved in hexane-ethanol (1:1, volume ratio), subjected to HPLC using CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd.), and eluted with hexane-ethanol (1:1 - 1:4, volume ratio) as a mobile phase at room temperature and at a flow rate 60 - 50 mL/min. The resulting fraction containing an optically active form having a shorter retention time was concentrated to give an amorphous form (9.08 g, 99.9% ee). The obtained amorphous form (4.72 g) was dissolved in ethanol (19 mL) and tetrahydrofuran (19 mL), 1N aqueous sodium hydroxide solution (18.6 mL) was added, and the mixture was stirred at room temperature for 20 min. The solvent was evaporated under reduced pressure. Water (40 mL) was added, and the mixture was neutralized with 1N hydrochloric acid (18.6 mL) under ice-cooling and stirred for 20 min. The resulting precipitate was

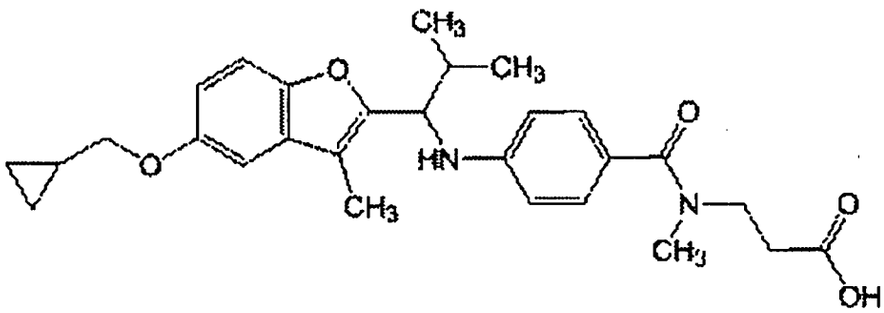
collected by filtration, and dried to give the title compound (4.27 g, 96%, 99.9% ee) as a colorless amorphous form.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.31 - 0.38 (m, 2 H), 0.58 - 0.68 (m, 2 H), 0.90 (d, J=6.8 Hz, 3 H), 1.12 (d, J=6.4 Hz, 3 H), 1.28 (s, 1 H), 2.17 - 2.29 (m, 4 H), 2.63 (t, J=6.4 Hz, 2 H), 3.01 (s, 3 H), 3.69 (t, J=6.4 Hz, 2 H), 3.82 (d, J=6.8 Hz, 2 H), 4.31 (d, J=7.5 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.78 - 6.89 (m, 2 H), 7.19 - 7.27 (m, 3 H).

[1044]

Example A78

3-[{[4-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1045]



[1046]

Ethyl 3-[{[4-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (18.23 g) obtained in Example A75(4) was dissolved in hexane-ethanol (1:1, volume ratio), subjected to HPLC using CHIRALPAK AD (50 mm ID×500 mmL, manufactured by Daicel Chemical Industries, Ltd.), and eluted with hexane-ethanol (1:1 - 1:4, volume ratio) as a mobile phase at room temperature and at a flow rate 60 - 50 mL/min. The resulting fraction containing an optically active form having a longer retention time was concentrated to give an amorphous form (9.08 g, 99.9% ee). The obtained amorphous form (4.73 g) was dissolved in ethanol (19 mL) and tetrahydrofuran (19 mL), 1N aqueous sodium hydroxide

solution (18.7 mL) was added, and the mixture was stirred at room temperature for 20 min. The solvent was evaporated under reduced pressure. Water (40 mL) was added, and the mixture was neutralized with 1N hydrochloric acid (18.7 mL) under ice-cooling and stirred for 30 min. The resulting precipitate was collected by filtration, and dried to give the title compound (4.02 g, 90%, 98.8% ee) as a colorless amorphous form. The obtained colorless amorphous (500 mg) was dissolved in ethyl acetate, and the mixture was washed with water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give a colorless amorphous. The obtained colorless amorphous was crystallized from ethyl acetate/hexane to give colorless crystals (401 mg). In addition, an amorphous product (60 mg) obtained by partitioning was crystallized from diethyl ether/hexane to give colorless crystals (45 mg).

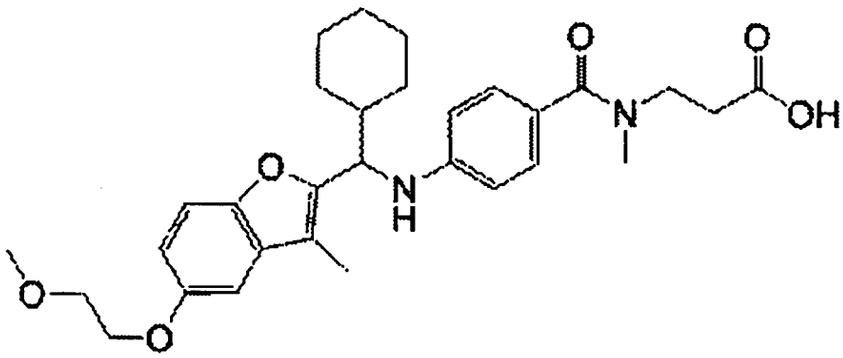
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.27 - 0.42 (m, 2 H), 0.56 - 0.66 (m, 2 H), 0.91 (d, J=6.8 Hz, 3 H), 1.12 (d, J=6.8 Hz, 3 H), 1.28 (s, 1 H), 2.18 - 2.28 (m, 4 H), 2.66 (t, J=6.4 Hz, 2 H), 3.03 (s, 3 H), 3.70 (t, J=6.6 Hz, 2 H), 3.82 (d, J=7.2 Hz, 2 H), 4.31 (d, J=7.5 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.73 - 6.89 (m, 2 H), 7.19 - 7.25 (m, 3 H).

[1047]

Example A79

3-[{[4-({cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1048]



[1049]

(1) 1-[2-hydroxy-5-(2-methoxyethoxy)phenyl]ethanone

To a solution (250 mL) of 1-(2,5-dihydroxyphenyl)ethanone (11.0 g) in acetonitrile were added 2-methoxyethylbromide (19.6 mL) and potassium carbonate (12.0 g) at room temperature, and the mixture was heated under reflux for 15 hr. The reaction mixture was allowed to cool to room temperature and filtered through celite, and the filtrate was concentrated under reduced pressure. Saturated aqueous ammonium chloride solution was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:10, volume ratio) to give the title object compound (7.6 g, 50%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.61 (s, 3 H), 3.46 (s, 3 H), 3.66 - 4.21 (m, 4 H), 6.92 (d, J=9.0 Hz, 1 H), 7.15 (d, J=9.0 Hz, 1 H), 7.22 - 7.26 (m, 1 H), 11.84 (s, 1 H).

[1050]

(2) cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methanone

1-[2-Hydroxy-5-(2-methoxyethoxy)phenyl]ethanone (7.0 g) synthesized in the above-mentioned (1) was dissolved in N,N-dimethylformamide (140 mL). Potassium carbonate (13.8 g) and 2-bromo-1-cyclohexylethanone (8.9 g) synthesized in Example A51(1) were added to the reaction mixture at room temperature, and the mixture was stirred for 15 hr. The reaction mixture was filtered through celite, water (200 mL) was added, and the mixture was extracted with diethyl ether (100 mL×2). The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide solution (100 mL), DBU (5.3 mL) was added at room temperature, and the mixture was stirred at 100°C for 1 hr. The reaction mixture was allowed to

cool to room temperature, 1N hydrochloric acid (100 mL) was added, and the mixture was extracted with diethyl ether (100 mL×2). The extract was washed with water, saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:20, volume ratio) to give the title object compound (10.3 g, 98%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.32 - 2.00 (m, 11 H), 2.56 (s, 3 H), 3.30 (d, J=3.4 Hz, 1 H), 3.48 (s, 3 H), 3.75 - 3.85 (m, 2 H), 4.15 - 4.25 (m, 2 H), 7.04 (d, J=2.5 Hz, 1 H), 7.13 (dd, J=8.9, 2.5 Hz, 1 H), 7.40 (d, J=8.9 Hz, 1 H).

[1051]

(3) cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methanol

Cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methanone (10.3 g) synthesized in the above-mentioned (2) was dissolved in a mixed solvent of tetrahydrofuran (180 mL) and methanol (20 mL). The reaction mixture was ice-cooled, and sodium borohydride (90%, 2.7 g) was added, and the reaction mixture was stirred at room temperature for 2 hr. The reaction mixture was ice-cooled again, water (10 mL) and 1N hydrochloric acid (100 mL) were carefully added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a crude product (10.3 g) of the title object compound as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.15 - 2.02 (m, 11 H), 2.56 (s, 3 H), 3.48 (s, 3 H), 3.73 - 3.87 (m, 2 H), 4.14 - 4.26 (m, 2 H), 4.44 -4.46 (m, 1 H), 7.04 (d, J=2.6 Hz, 1 H), 7.13 (dd, J=9.0, 2.6 Hz, 1 H), 7.40 (d, J=9.0 Hz, 1 H).

[1052]

(4) ethyl 3-[{[4-({cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-

yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

To a solution (200 mL) of cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methanol (10.3 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added thionyl chloride (4.7 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min and ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (100 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (150 mL), sodium iodide (8.0 g), sodium carbonate (5.3 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (8.9 g) synthesized in Example 2(2) were added, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (8.5 g, 43%) as a yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 2.14 (m, 14 H), 2.21 (s, 3 H), 2.61 (t, J=6.8 Hz, 2 H), 3.01 (s, 3 H), 3.46 (s, 3 H), 3.60 - 3.81 (m, 4 H), 4.01 - 4.21 (m, 4 H), 4.27 - 4.46 (m, 2 H), 6.56 (d, J=8.3 Hz, 2 H), 6.76 - 6.95 (m, 2 H), 7.14 - 7.25 (m, 3 H).

[1053]

(5) 3-[{[4-({cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

Ethyl 3-[{[4-({cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (5.4 g) synthesized in the above-mentioned (4) was dissolved in ethanol (150 mL), 1N aqueous sodium hydroxide solution (15 mL)

was added at room temperature, and the mixture was stirred at 50°C for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (20 mL) was added to the residue, and the mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (3.0 g, 59%) as a white solid.

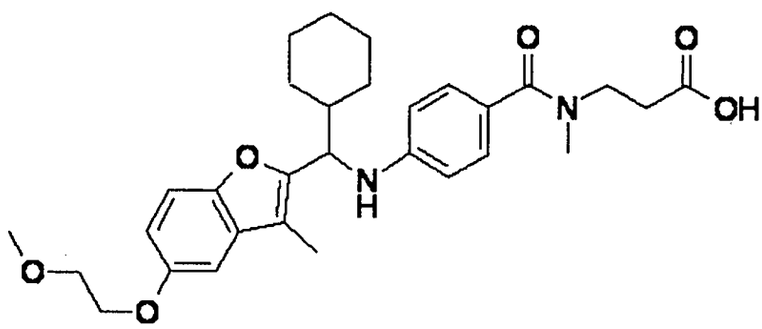
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 2.14 (m, 12 H), 2.21 (s, 3 H), 2.66 (t, J=6.1 Hz, 2 H), 3.03 (s, 3 H), 3.46 (s, 3 H), 3.60 - 3.81 (m, 4 H), 4.01 - 4.21 (m, 4 H), 4.35 (d, J=7.8 Hz, 2 H), 6.55 (d, J=8.7 Hz, 2 H), 6.76 - 6.95 (m, 2 H), 7.14 - 7.25 (m, 3 H).

[1054]

Example A80

3-[{[4-({cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1055]




[1056]

3-[{[4-({cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

3-[{[4-({Cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid (3.0 g) synthesized in Example A79(5) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (5mm i.d.×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/2-propanol/trifluoroacetic acid

(500/500/1), flow rate: 60 mL/min, column temperature: 30°C). To the fraction containing an optically active form having a shorter retention time under the above-mentioned high performance liquid chromatography conditions was added triethylamine (10 mL) and the mixture was concentrated to give a triethylamine salt (3.7 g) of the title object compound. 1N Hydrochloric acid (30 mL) was added thereto, and the mixture was extracted with diethyl ether. The extract was washed with water and saturated brine, dried over magnesium sulfate and concentrated under reduced pressure to give the title object compound (1.49 g, 99.9% ee) as a white solid.

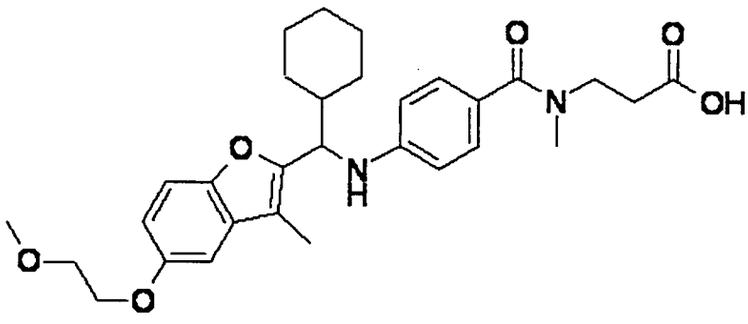
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 2.14 (m, 12 H), 2.21 (s, 3 H), 2.66 (t, J=6.1 Hz, 2 H), 3.03 (s, 3 H), 3.46 (s, 3 H), 3.60 - 3.81 (m, 4 H), 4.01 - 4.21 (m, 4 H), 4.35 (d, J=7.8 Hz, 2 H), 6.55 (d, J=8.7 Hz, 2 H), 6.76 - 6.95 (m, 2 H), 7.14 - 7.25 (m, 3 H).

[1057]

Example A81

3-[{[4-({cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1058]



[1059]

(1) 3-[{[4-({cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

3-[{[4-({Cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

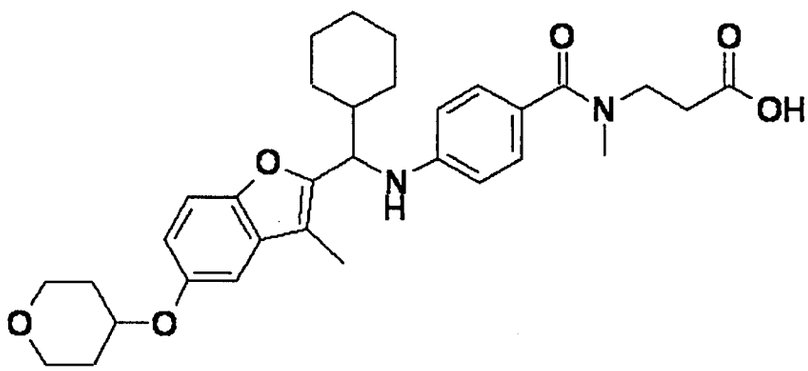
(3.0 g) synthesized in Example A79(5) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50mm i.d.×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/2-propanol/trifluoroacetic acid (500/500/1), flow rate: 60 mL/min, column temperature: 30°C). To the fraction containing an optically active form having a longer retention time under the above-mentioned high performance liquid chromatography conditions was added triethylamine (30 mL), and the mixture was concentrated to give a triethylamine salt (9.2 g) of the title object compound. 1N Hydrochloric acid (30 mL) was added thereto, and the mixture was extracted with diethyl ether. The extract was washed with water and saturated brine, dried over magnesium sulfate and concentrated under reduced pressure to give the title object compound (1.50 g, 99.9% ee) as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 2.14 (m, 12 H), 2.21 (s, 3 H), 2.66 (t, J=6.1 Hz, 2 H), 3.03 (s, 3 H), 3.46 (s, 3 H), 3.60 - 3.81 (m, 4 H), 4.01 - 4.21 (m, 4 H), 4.35 (d, J=7.8 Hz, 2 H), 6.55 (d, J=8.7 Hz, 2 H), 6.76 - 6.95 (m, 2 H), 7.14 - 7.25 (m, 3 H).

[1060]

Example A82

3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1061]




[1062]

(1) 1-[5-(benzyloxy)-2-hydroxyphenyl]ethanone

To a solution (400 mL) of 1-(2,5-dihydroxyphenyl)ethanone (25.0 g) in acetonitrile were added benzylbromide (19.6 mL) and potassium carbonate (25.0 g) at room temperature, and the mixture was heated under reflux for 2 hr. The reaction mixture was allowed to cool to room temperature, filtered through celite, and the filtrate was concentrated under reduced pressure. Saturated aqueous ammonium chloride solution was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a solid. The obtained solid was washed with ethanol-isopropyl ether to give the title object compound (31.0 g, 80%) as a yellow-green solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.58 (s, 3 H), 5.05 (s, 2 H), 7.11 - 7.53 (m, 8 H), 11.85 (s, 1 H).

[1063]

(2) [5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methanone

To a solution (500 mL) of 1-[5-(benzyloxy)-2-hydroxyphenyl]ethanone (29.5 g) synthesized in the above-mentioned (1) in N,N-dimethylformamide were added potassium carbonate (41.4 g) and 2-bromo-1-cyclohexylethanone (25.0 g) synthesized in Example A51(1) at room temperature, and the mixture was stirred at 60°C for 15 hr. The reaction mixture was allowed to cool to room temperature, filtered through celite. Water was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a solid. The obtained solid was washed with ethanol-isopropyl ether to give the title object compound (18.0 g, 43%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.17 - 2.10 (m, 10 H), 2.56 (s, 3 H), 3.17 - 3.43 (m, 1 H), 5.12 (s, 2 H), 7.04 - 7.21 (m, 2 H), 7.30 - 7.51 (m, 6 H).

[1064]

(3) cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methanone

[5-(Benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methanone (7.3 g) synthesized in the above-mentioned (2) was dissolved in a ethanol (150 mL) and tetrahydrofuran (30 mL), and palladium carbon-ethylenediamine complex (1.0 g) was added at room temperature. The reaction mixture was stirred at 60°C for 3 hr under hydrogen atmosphere (1 atm), allowed to cool to room temperature, and the catalyst was filtered. The filtrate was concentrated under reduced pressure to give a crude product (5.2 g, quantitative) of the title object compound as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.21 - 2.03 (m, 10 H), 2.54 (s, 3 H), 3.22 - 3.38 (m, 1 H), 4.78 (br. s., 1 H), 6.96 - 7.05 (m, 2 H), 7.38 (d, J=9.5 Hz, 1 H).

[1065]

(4) cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methanone

Cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methanone (5.2 g) synthesized in the above-mentioned (3) was dissolved in dimethylformamide (100 mL), and potassium phosphate (7.4 g) and tetrahydro-2H-pyran-4-yl 4-methylbenzenesulfonate (9.0 g) synthesized by the method of EP-A-1367058 were added to the mixture at room temperature, and the mixture was stirred at 80°C overnight. The reaction mixture was allowed to cool to room temperature, water (150 mL) was added and the mixture was extracted with diethyl ether (100 mL×2). The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:10, volume ratio) to give the title object compound (7.1 g, 99%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.35 - 2.10 (m, 14 H), 2.56 (s, 3 H), 3.24 - 3.38 (m, 1 H), 3.50 - 3.65 (m, 2 H), 3.95 - 4.07 (m, 2 H), 4.50 (tt, J=7.8, 3.9 Hz, 1 H), 7.04 - 7.16 (m, 2 H), 7.42 (d, J=8.7 Hz, 1 H).

[1066]

(5) cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methanol

Cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methanone (7.1 g) synthesized in the above-mentioned (4) was dissolved in tetrahydrofuran (200 mL) and methanol (20 mL), and sodium borohydride (90%, 1.6 g) was added under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 2 hr. The reaction mixture was ice-cooled again, water (10 mL) and 1N hydrochloric acid (100 mL) were added carefully, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a crude product (6.7 g, 98%) of the title object compound as a pale-yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.82 - 2.14 (m, 15 H), 2.18 (s, 3 H), 3.57 (ddd, J=11.6, 8.4, 3.4 Hz, 2 H), 3.93 - 4.06 (m, 2 H), 4.36 - 4.59 (m, 2 H), 6.89 (dd, J=8.7, 2.3 Hz, 1 H), 6.97 (d, J=2.3 Hz, 1 H), 7.31 (d, J=8.7 Hz, 1 H).

[1067]

(6) ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

Cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methanol (6.7 g) synthesized in the above-mentioned (5) was dissolved in tetrahydrofuran (120 mL), and thionyl chloride (2.6 mL) was added at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (100 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (100 mL), sodium iodide (5.3 g), sodium

carbonate (3.5 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (4.9 g) synthesized in Example 2(2) were added, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (6.1 g, 54%) as a yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 2.10 (m, 18 H), 2.21 (s, 3 H), 2.61 (t, J=7.0 Hz, 2 H), 3.01 (s, 3 H), 3.55 (ddd, J=11.7, 8.5, 3.2 Hz, 2 H), 3.70 (t, J=7.0 Hz, 2 H), 3.90 - 4.05 (m, 2 H), 4.27 - 4.52 (m, 4 H), 6.56 (d, J=8.7 Hz, 2 H), 6.77 - 6.96 (m, 2 H), 7.15 - 7.25 (m, 3 H).

[1068]

(7) 3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

Ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.6 g) synthesized in the above-mentioned (6) was dissolved in ethanol (20 mL), 1N aqueous sodium hydroxide solution (3 mL) was added at room temperature, and the mixture was stirred at room temperature for 12 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (3 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from acetone to give the title object compound (0.5 g, 77%) as colorless crystals.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 - 2.14 (m, 15 H), 2.21 (s, 3 H), 2.67 (t, J=6.2 Hz, 2 H), 3.03 (s, 3 H), 3.56 (ddd, J=11.6, 8.4, 3.0 Hz, 2 H), 3.69 (t, J=6.6 Hz, 2 H), 3.88 - 4.08 (m, 2 H), 4.27 - 4.53 (m, 2 H), 6.55 (d, J=8.7 Hz, 2 H), 6.78 - 6.99

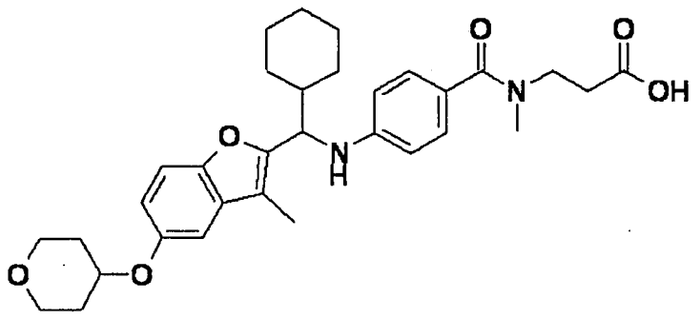
(m, 2 H), 7.17 - 7.26 (m, 3 H).

[1069]

Example A83

3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1070]



[1071]

(1) ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

Ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (4.0 g) synthesized in Example A82(6) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50mm i.d.×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/ethanol (200/800), flow rate: 60 mL/min, column temperature: 30°C). The fraction containing an optically active form having a shorter retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give the title object compound (1.8 g, 99.9% ee).

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 2.10 (m, 18 H), 2.21 (s, 3 H), 2.61 (t, J=7.0 Hz, 2 H), 3.01 (s, 3 H), 3.55 (ddd, J=11.7, 8.5, 3.2 Hz, 2 H), 3.70 (t, J=7.0 Hz, 2 H), 3.90 - 4.05 (m, 2 H), 4.27 - 4.52 (m, 4 H), 6.56 (d, J=8.7 Hz, 2 H), 6.77 - 6.96 (m, 2 H), 7.15 - 7.25 (m, 3 H).

[1072]

(2)3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

Ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (1.8 g) optically resolved in the above-mentioned (1) was dissolved in ethanol (20 mL), 1N aqueous sodium hydroxide solution (5 mL) was added at room temperature, and the mixture was stirred at 50°C for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (5 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from acetone to give the title object compound (1.6 g, 95%, 99.9% ee) as colorless crystals.

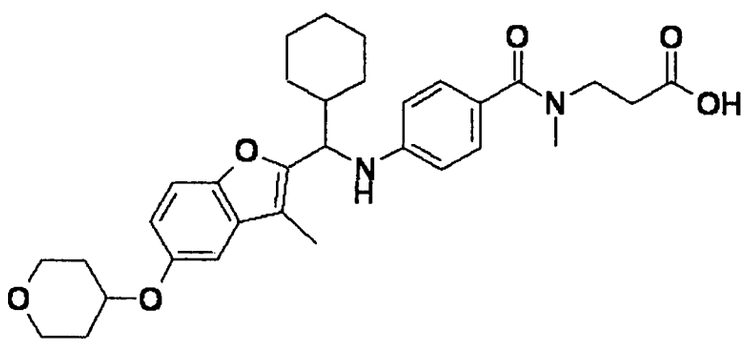
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 - 2.14 (m, 15 H), 2.21 (s, 3 H), 2.67 (t, J=6.2 Hz, 2 H), 3.03 (s, 3 H), 3.56 (ddd, J=11.6, 8.4, 3.0 Hz, 2 H), 3.69 (t, J=6.6 Hz, 2 H), 3.88 - 4.08 (m, 2 H), 4.27 - 4.53 (m, 2 H), 6.55 (d, J=8.7 Hz, 2 H), 6.78 - 6.99 (m, 2 H), 7.17 - 7.26 (m, 3 H).

[1073]

Example A84

3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1074]



[1075]

(1) ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

Ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (4.0 g) synthesized in Example A82(6) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50mm i.d.×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/ethanol (200/800), flow rate: 60 mL/min, column temperature: 30°C). The fraction containing an optically active form having a longer retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give the title object compound (1.8 g, 99.9% ee).

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 2.10 (m, 18 H), 2.21 (s, 3 H), 2.61 (t, J=7.0 Hz, 2 H), 3.01 (s, 3 H), 3.55 (ddd, J=11.7, 8.5, 3.2 Hz, 2 H), 3.70 (t, J=7.0 Hz, 2 H), 3.90 - 4.05 (m, 2 H), 4.27 - 4.52 (m, 4 H), 6.56 (d, J=8.7 Hz, 2 H), 6.77 - 6.96 (m, 2 H), 7.15 - 7.25 (m, 3 H).

[1076]

(2)3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

Ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (1.8 g) optically resolved in the above-mentioned (1) was dissolved in ethanol (20 mL), 1N aqueous sodium hydroxide solution (5 mL) was added at room temperature, and the mixture was stirred at 50°C for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (5 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract

was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from acetone to give the title object compound (1.5 g, 88%,99.9% ee) as colorless crystals.

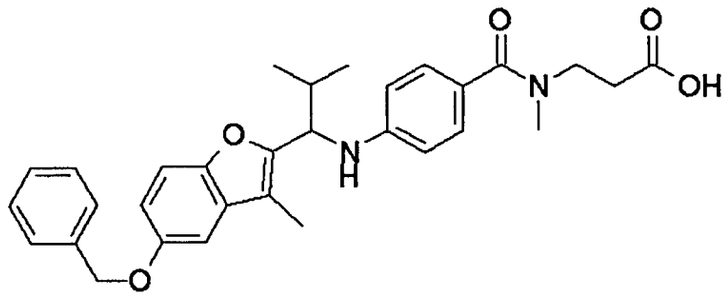
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 - 2.14 (m, 15 H), 2.21 (s, 3 H), 2.67 (t, J=6.2 Hz, 2 H), 3.03 (s, 3 H), 3.56 (ddd, J=11.6, 8.4, 3.0 Hz, 2 H), 3.69 (t, J=6.6 Hz, 2 H), 3.88 - 4.08 (m, 2 H), 4.27 - 4.53 (m, 2 H), 6.55 (d, J=8.7 Hz, 2 H), 6.78 - 6.99 (m, 2 H), 7.17 - 7.26 (m, 3 H).

[1077]

Example A85

3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1078]



[1079]

(1)1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-one

To a solution (200 mL) of 1-[5-(benzyloxy)-2-hydroxyphenyl]ethanone (16.1 g) synthesized in Example A82(1) in N,N-dimethylformamide were added at room temperature potassium carbonate (27.6 g) and 1-bromo-3-methylbutan-2-one (14.3 g) synthesized in Example A75(1), and the mixture was stirred for 15 hr. The reaction mixture was filtered through celite, water (200 mL) was added and the mixture was extracted with diethyl ether (100 mL×2). The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved

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in N,N-dimethylformamide (100 mL), and DBU (9.9 mL) was added at room temperature. The reaction mixture was stirred at 100°C for 1 hr. The reaction mixture was allowed to cool to room temperature, 1N hydrochloric acid (150 mL) was added, and the mixture was extracted with diethyl ether (100 mL×2). The extract was washed with water, saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethanol-diisopropyl ether to give the title object compound (11.7 g, 57%) as pale-yellow crystals.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.23 (d, J=6.8 Hz, 6 H), 2.57 (s, 3 H), 3.57 (dt, J=13.8, 6.8 Hz, 1 H), 5.12 (s, 2 H), 7.11 (d, J=2.6 Hz, 1 H), 7.13 - 7.21 (m, 1 H), 7.30 - 7.55 (m, 6 H).

[1080]

(2)1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-ol

1-[5-(Benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-one (11.7 g) synthesized in the above-mentioned (1) was dissolved in a tetrahydrofuran (150 mL) and methanol (15 mL), and sodium borohydride (90%, 3.0 g) was added under ice-cooling. The ice bath was removed, the reaction mixture was stirred at room temperature for 2 hr. The mixture was ice-cooled again, water (10 mL) and 1N hydrochloric acid (100 mL) were carefully added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (11.3 g, quantitative) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.82 (d, J=6.8 Hz, 3 H), 1.12 (d, J=6.8 Hz, 3 H), 1.55 (d, J=2.6 Hz, 1 H), 2.11 - 2.34 (m, 4 H), 4.46 (dd, J=8.3, 6.0 Hz, 1 H), 5.10 (s, 2 H), 6.82 - 7.08 (m, 2 H), 7.28 - 7.55 (m, 6 H).

[1081]

(3) ethyl 3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

1-[5-(Benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-ol (10.2 g) synthesized in the above-mentioned (2) was dissolved in tetrahydrofuran (150 mL), and thionyl chloride (4.3 mL) was added at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (100 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (200 mL), sodium iodide (7.4 g), sodium carbonate (5.0 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (8.2 g) synthesized in Example 2(2) were added, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (6.3 g, 35%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.8 Hz, 3 H), 1.12 (d, J=6.8 Hz, 3 H), 1.23 (t, J=7.2 Hz, 3 H), 2.13 - 2.33 (m, 4 H), 2.61 (t, J=7.2 Hz, 2 H), 3.01 (s, 3 H), 3.71 (t, J=7.2 Hz, 2 H), 4.12 (q, J=7.2 Hz, 2 H), 4.25 - 4.46 (m, 2 H), 5.09 (s, 2 H), 6.57 (d, J=8.7 Hz, 2 H), 6.81 - 7.02 (m, 2 H), 7.15 - 7.25 (m, 3 H), 7.30 - 7.59 (m, 5 H).

[1082]

(4)3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

Ethyl 3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-

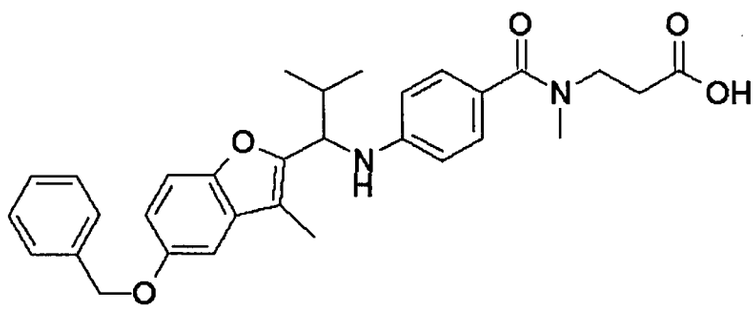
yl]-2-
methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.38 g) synthesized in the above-mentioned (3) was dissolved in ethanol (5 mL), 1N aqueous sodium hydroxide solution (1.5 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (1.5 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethanol-water to give the title object compound (0.28 g, 79%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.8 Hz, 3 H), 1.12 (d, J=6.8 Hz, 3 H), 2.18 - 2.30 (m, 4 H), 2.66 (t, J=6.2 Hz, 2 H), 3.03 (s, 3 H), 3.69 (t, J=6.2 Hz, 2 H), 4.32 (d, J=7.5 Hz, 1 H), 5.08 (s, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.83 - 7.02 (m, 2 H), 7.17 - 7.26 (m, 3 H), 7.30 - 7.53 (m, 5 H).

[1083]

Example A86

3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1084]



[1085]

(1) ethyl 3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

Ethyl 3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-

yl]-2-
methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (3.0 g) synthesized in Example A85(3) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50mm i.d.×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/ethanol (200/800), flow rate: 60 mL/min, column temperature: 30°C). The fraction containing an optically active form having a longer retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give the title object compound (1.23 g, 99.9% ee).

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.8 Hz, 3 H), 1.12 (d, J=6.8 Hz, 3 H), 1.23 (t, J=7.2 Hz, 3 H), 2.13 - 2.33 (m, 4 H), 2.61 (t, J=7.2 Hz, 2 H), 3.01 (s, 3 H), 3.71 (t, J=7.2 Hz, 2 H), 4.12 (q, J=7.2 Hz, 2 H), 4.25 - 4.46 (m, 2 H), 5.09 (s, 2 H), 6.57 (d, J=8.7 Hz, 2 H), 6.81 - 7.02 (m, 2 H), 7.15 - 7.25 (m, 3 H), 7.30 - 7.59 (m, 5 H).

[1086]

(2)3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

Ethyl 3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (1.23 g)optically resolved in the above-mentioned (1) was dissolved in ethanol (15 mL), 1N aqueous sodium hydroxide solution (4 mL) was added at room temperature, and the mixture was stirred at 50°C for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (4 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethanol-water to give the title object compound (1.22 g, 95%, 99.9% ee) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.8 Hz, 3 H), 1.12 (d,

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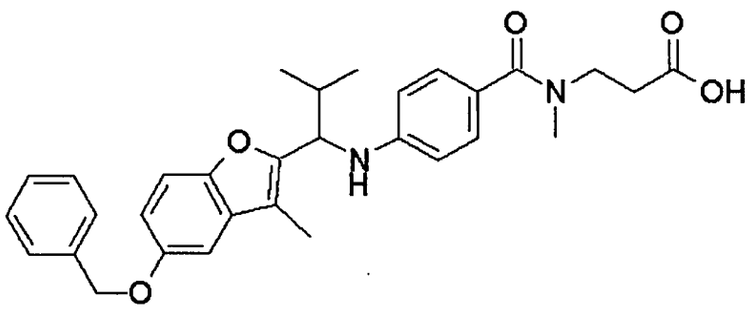
J=6.8 Hz, 3 H), 2.18 - 2.30 (m, 4 H), 2.66 (t, J=6.2 Hz, 2 H), 3.03 (s, 3 H), 3.69 (t, J=6.2 Hz, 2 H), 4.32 (d, J=7.5 Hz, 1 H), 5.08 (s, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.83 - 7.02 (m, 2 H), 7.17 - 7.26 (m, 3 H), 7.30 - 7.53 (m, 5 H).

[1087]

Example A87

3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1088]



[1089]

(1) ethyl 3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

Ethyl 3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (3.0 g) synthesized in Example A85(3) was fractionated by high performance liquid chromatography (column: CHIRALPAK AD (50mm i.d.×500 mmL, manufactured by Daicel Chemical Industries, Ltd., mobile phase: hexane/ethanol (200/800), flow rate: 60 mL/min, column temperature: 30°C). The fraction containing an optically active form having a shorter retention time under the above-mentioned high performance liquid chromatography conditions was concentrated to give the title object compound (1.25 g, 99.9% ee).

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.8 Hz, 3 H), 1.12 (d, J=6.8 Hz, 3 H), 1.23 (t, J=7.2 Hz, 3 H), 2.13 - 2.33 (m, 4 H),

2.61 (t, J=7.2 Hz, 2 H), 3.01 (s, 3 H), 3.71 (t, J=7.2 Hz, 2 H), 4.12 (q, J=7.2 Hz, 2 H), 4.25 - 4.46 (m, 2 H), 5.09 (s, 2 H), 6.57 (d, J=8.7 Hz, 2 H), 6.81 - 7.02 (m, 2 H), 7.15 - 7.25 (m, 3 H), 7.30 - 7.59 (m, 5 H).

[1090]

(2)3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

Ethyl 3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (1.25 g) optically resolved in the above-mentioned (1) was dissolved in ethanol (15 mL), 1N aqueous sodium hydroxide solution (4 mL) was added at room temperature, and the mixture was stirred at 50°C for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (4 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethanol-water to give the title object compound (1.08 g, 93%, 99.9% ee) as a colorless solid.

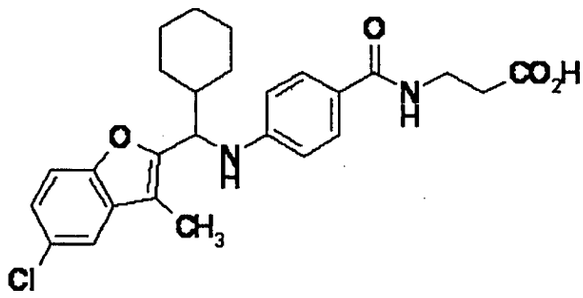
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.8 Hz, 3 H), 1.12 (d, J=6.8 Hz, 3 H), 2.18 - 2.30 (m, 4 H), 2.66 (t, J=6.2 Hz, 2 H), 3.03 (s, 3 H), 3.69 (t, J=6.2 Hz, 2 H), 4.32 (d, J=7.5 Hz, 1 H), 5.08 (s, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.83 - 7.02 (m, 2 H), 7.17 - 7.26 (m, 3 H), 7.30 - 7.53 (m, 5 H).

[1091]

Example A88

3-{[(4-{[(5-chloro-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1092]



[1093]

(1) 5-chloro-N-methoxy-N,3-dimethyl-1-benzofuran-2-carboxamide

To a solution (50 mL) of 1-(5-chloro-2-hydroxyphenyl)ethanone (5.00 g) in tetrahydrofuran were added potassium carbonate (8.10 g), sodium iodide (8.78 g) and 2-chloro-N-methoxy-N-methylacetamide (4.43 g), and the mixture was stirred overnight with heating under reflux. Insoluble material was filtered off, and the filtrate was concentrated under reduced pressure to give a white solid. To a solution (50 mL) of the obtained solid in N,N-dimethylformamide was added 1,8-diazabicyclo[5.4.0]undec-7-ene (4.38 mL), and the mixture was stirred at 120°C for 2 hr. The reaction mixture was cooled to room temperature, 1N hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30% ethyl acetate/hexane) to give the title object compound (2.15 g, 29%) as a brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.47 (s, 3 H), 3.38 (s, 3 H), 3.86 (s, 3 H), 7.35 (dd, J=8.9, 1.8 Hz, 1 H), 7.40 (dd, J=8.9, 0.6 Hz, 1 H), 7.57 (dd, J=1.8, 0.6 Hz, 1 H).

[1094]

(2) 5-chloro-3-methyl-1-benzofuran-2-carbaldehyde

To a solution (40 mL) of 5-chloro-N-methoxy-N,3-dimethyl-1-benzofuran-2-carboxamide (2.15 g) synthesized above in tetrahydrofuran was added lithium aluminum hydride (322 mg) at

0°C, and the mixture was stirred for 1 hr. Water (320 µL) was added to quench the reaction, 1N aqueous sodium hydroxide solution (320 µL) was added, and the mixture was stirred at room temperature for 1 hr. The resulting insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (tetrahydrofuran) to give a pale-yellow solid. The obtained solid was washed with diisopropyl ether to give the title object compound (1.21 g, 73%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.60 (s, 3 H), 7.43 - 7.51 (m, 2 H), 7.65 - 7.67 (m, 1 H), 10.02 (s, 1 H).

[1095]

(3)(5-chloro-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methanol

To a solution (10 mL) of 5-chloro-3-methyl-1-benzofuran-2-carbaldehyde (600 mg) synthesized above in tetrahydrofuran was added a 1.0M solution (4.62 mL) of cyclohexylmagnesium bromide in tetrahydrofuran at 0°C, and the mixture was stirred for 1 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15% ethyl acetate/hexane) to give the title object compound (518 mg, 60%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 - 1.41 (m, 6 H), 1.61 - 1.71 (m, 2 H), 1.75 - 1.98 (m, 3 H), 2.09 - 2.18 (m, 1 H), 2.19 (s, 3 H), 4.52 (dd, J=8.4, 6.0 Hz, 1 H), 7.20 (dd, J=8.4, 2.1 Hz, 1 H), 7.33 (dd, J=8.4, 0.6 Hz, 1 H), 7.42 (dd, J=2.1, 0.6 Hz, 1 H).

[1096]

(4)5-chloro-2-[chloro(cyclohexyl)methyl]-3-methyl-1-benzofuran

To a solution (10 mL) of (5-chloro-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methanol (518 mg) synthesized above in

toluene was added thionyl chloride (163 μL), and the mixture was stirred at 100°C for 1 hr. The reaction mixture was poured into ice-cooled saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (553 mg, quantitative) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.83 - 1.48 (m, 6 H), 1.60 - 1.71 (m, 2 H), 1.77 - 1.87 (m, 1 H), 2.10 - 2.24 (m, 4 H), 2.27 - 2.37 (m, 1 H), 4.78 (d, J=9.6 Hz, 1 H), 7.20 - 7.26 (m, 1 H), 7.34 - 7.38 (m, 1 H), 7.42 - 7.44 (m, 1 H).

[1097]

(5)3-{[(4-{[(5-chloro-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

A mixture of 5-chloro-2-[chloro(cyclohexyl)methyl]-3-methyl-1-benzofuran (270 mg) synthesized above, ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (215 mg) synthesized in Example 1(2), sodium iodide (204 mg), sodium carbonate (144 mg) and N,N-dimethylformamide (10 mL) was stirred overnight at 80°C. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% ethyl acetate/hexane) to give a pale-yellow oil. To a mixture of the obtained oil, tetrahydrofuran (5 mL) and ethanol (5 mL) 1N aqueous sodium hydroxide solution (1.00 mL) was added, and the mixture was stirred at room temperature for 2 hr, and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (132

mg, 31%) as a yellow solid.

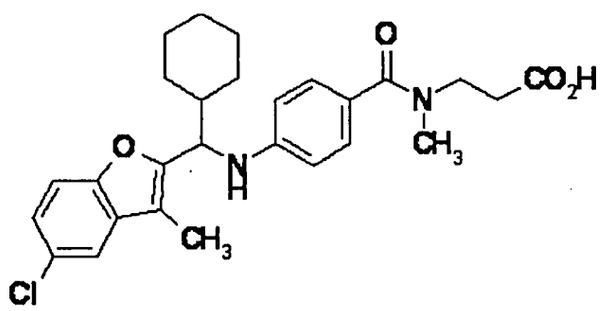
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.35 (m, 5 H), 1.44 - 1.55 (m, 1 H), 1.60 - 1.96 (m, 4 H), 2.01 - 2.12 (m, 1 H), 2.20 (s, 3 H), 2.54 - 2.67 (m, 2 H), 3.56 - 3.68 (m, 2 H), 4.37 (d, J=7.9 Hz, 1 H), 6.50 - 6.66 (m, 3 H), 7.12 - 7.18 (m, 1 H), 7.23 - 7.30 (m, 1 H), 7.37 (d, J=1.9 Hz, 1 H), 7.52 (d, J=8.7 Hz, 2 H).

[1098]

Example A89

3-{[(4-{[(5-chloro-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[1099]



[1100]

A mixture of 5-chloro-2-[chloro(cyclohexyl)methyl]-3-methyl-1-benzofuran (283 mg) synthesized in Example A88(4), ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (238 mg) synthesized in Example 2(2), sodium iodide (214 mg), sodium carbonate (152 mg) and N,N-dimethylformamide (10 mL) was stirred overnight at 80°C. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (40% ethyl acetate/hexane) to give a pale-yellow oil. To a mixture of the obtained oil, tetrahydrofuran

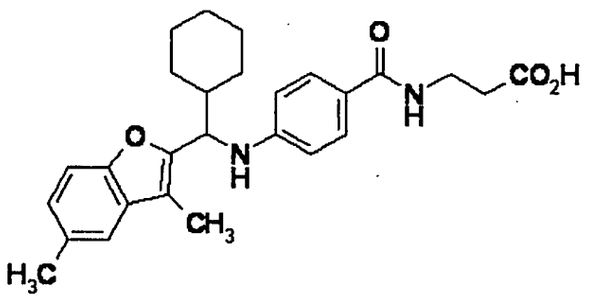
(5 mL) and ethanol (5 mL) 1N aqueous sodium hydroxide solution (1.00 mL) was added, and the mixture was stirred at room temperature for 1.5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (113 mg, 25%) as a yellow solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.38 (m, 5 H), 1.45 - 1.56 (m, 1 H), 1.61 - 1.97 (m, 4 H), 2.02 - 2.13 (m, 1 H), 2.21 (s, 3 H), 2.60 - 2.69 (m, 2 H), 3.01 (s, 3 H), 3.68 (t, J=6.2 Hz, 2 H), 4.36 (d, J=7.9 Hz, 1 H), 6.54 (d, J=8.7 Hz, 2 H), 7.13 - 7.19 (m, 1 H), 7.20 - 7.31 (m, 3 H), 7.38 (d, J=1.9 Hz, 1 H).

[1101]

Example A90

3-{[(4-{[cyclohexyl(3,5-dimethyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1102]




[1103]

(1)N-methoxy-N,3,5-trimethyl-1-benzofuran-2-carboxamide

To a solution (50 mL) of 1-(2-hydroxy-5-methylphenyl)ethanone (5.00 g) in N,N-dimethylformamide were added potassium carbonate (9.20 g), sodium iodide (9.98 g) and 2-chloro-N-methoxy-N-methylacetamide (5.04 g), and the mixture was stirred at 50°C for 5 hr then at 80°C overnight. The insoluble material was filtered off, 1,8-diazabicyclo[5.4.0]undec-7-ene (5.00 mL) was added to the filtrate and the mixture was stirred at 120°C for 2 hr. 1N

Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give the title object compound (3.78 g, 49%) as a brown oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3 H), 2.49 (s, 3 H), 3.38 (s, 3 H), 3.86 (s, 3 H), 7.19 - 7.24 (m, 1 H), 7.32 - 7.34 (m, 1 H), 7.35 - 7.39 (m, 1 H).

[1104]

(2)3,5-dimethyl-1-benzofuran-2-carbaldehyde

To a solution (50 mL) of N-methoxy-N,3,5-trimethyl-1-benzofuran-2-carboxamide (3.78 g) synthesized above in tetrahydrofuran was added lithium aluminum hydride (307 mg) at -78°C, and the mixture was stirred for 2 hr. Water (350 μL) was added to quench the reaction, 1N aqueous sodium hydroxide solution (700 μL) was added, and the mixture was stirred at room temperature for 1 hr. The resulting insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was washed with hexane to give the title object compound (2.08 g, 74%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.48 (s, 3 H), 2.60 (s, 3 H), 7.30 - 7.35 (m, 1 H), 7.40 - 7.47 (m, 2 H), 10.01 (s, 1 H).

[1105]

(3)cyclohexyl(3,5-dimethyl-1-benzofuran-2-yl)methanol

To a solution (20 mL) of 3,5-dimethyl-1-benzofuran-2-carbaldehyde (1.00 g) synthesized above in tetrahydrofuran was added a 1.0M solution (8.61 mL) of cyclohexylmagnesium bromide in tetrahydrofuran at 0°C, and the mixture was stirred for 1 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, tetrahydrofuran was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography

(25% ethyl acetate/hexane) to give the title object compound (1.13 g, 76%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.83 - 0.99 (m, 1 H), 1.00 - 1.44 (m, 5 H), 1.58 - 1.70 (m, 2 H), 1.74 - 1.98 (m, 3 H), 2.09 - 2.22 (m, 4 H), 2.45 (s, 3 H), 4.51 (dd, J=8.5, 5.9 Hz, 1 H), 7.03 - 7.11 (m, 1 H), 7.23 - 7.33 (m, 2 H).

[1106]

(4)2-[chloro(cyclohexyl)methyl]-3,5-dimethyl-1-benzofuran

To a solution (20 mL) of cyclohexyl(3,5-dimethyl-1-benzofuran-2-yl)methanol (1.13 g) synthesized above in toluene pyridine (424 μL) and thionyl chloride (382 μL) were added, and the mixture was stirred at room temperature for 5 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (1.12 g, 93%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.82 - 0.97 (m, 1 H), 1.00 - 1.40 (m, 4 H), 1.41 - 1.51 (m, 1 H), 1.59 - 1.70 (m, 2 H), 1.76 - 1.87 (m, 1 H), 2.11 - 2.25 (m, 4 H), 2.28 - 2.38 (m, 1 H), 2.44 (s, 3 H), 4.80 (d, J=9.3 Hz, 1 H), 7.07 - 7.12 (m, 1 H), 7.23 - 7.26 (m, 1 H), 7.32 (d, J=8.4 Hz, 1 H).

[1107]

(5)3-{[(4-{[cyclohexyl(3,5-dimethyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

A mixture of 2-[chloro(cyclohexyl)methyl]-3,5-dimethyl-1-benzofuran (400 mg) synthesized above, ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (343 mg) synthesized in Example 1(2), sodium iodide (327 mg), sodium carbonate (231 mg) and N,N-dimethylformamide (10 mL) was stirred at 80°C for 5 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified

by silica gel column chromatography (45% ethyl acetate/hexane) to give a yellow oil. To a mixture of the obtained oil, tetrahydrofuran (5 mL) and ethanol (5 mL) 1N aqueous sodium hydroxide solution (2.00 mL) were added, and the mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (436 mg, 67%) as a white solid.

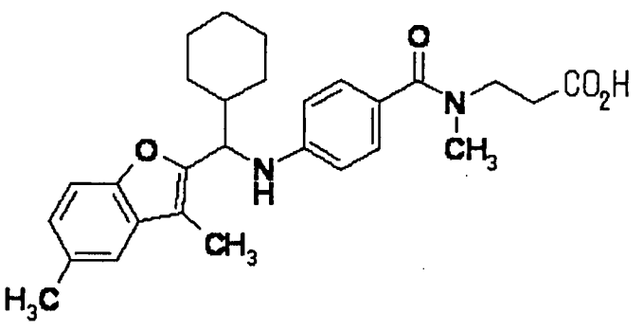
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.36 (m, 5 H), 1.47 - 1.58 (m, 1 H), 1.59 - 1.97 (m, 4 H), 2.02 - 2.12 (m, 1 H), 2.22 (s, 3 H), 2.42 (s, 3 H), 2.61 - 2.69 (m, 2 H), 3.60 - 3.70 (m, 2 H), 4.38 (d, J=8.0 Hz, 1 H), 6.49 - 6.60 (m, 3 H), 7.00 - 7.06 (m, 1 H), 7.19 - 7.24 (m, 2 H), 7.52 (d, J=7.6 Hz, 2 H).

[1108]

Example A91

3-{[(4-{[cyclohexyl(3,5-dimethyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1109]




[1110]

(1) ethyl 3-{[(4-{[cyclohexyl(3,5-dimethyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

A mixture of 2-[chloro(cyclohexyl)methyl]-3,5-dimethyl-1-benzofuran (400 mg) synthesized in Example A90(4), ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (363 mg) synthesized in Example 2(2), sodium iodide (327 mg), sodium carbonate (231 mg) and N,N-dimethylformamide (10 mL) was

stirred at 80°C for 5 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (45% ethyl acetate/hexane) to give the title object compound (471 mg, 66%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.36 (m, 8 H), 1.48 - 1.59 (m, 1 H), 1.60 - 1.96 (m, 4 H), 2.03 - 2.13 (m, 1 H), 2.22 (s, 3 H), 2.42 (s, 3 H), 2.57 - 2.65 (m, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.1 Hz, 2 H), 4.07 - 4.17 (m, 2 H), 4.32 - 4.40 (m, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 7.03 (dd, J=8.3, 1.3 Hz, 1 H), 7.17 - 7.24 (m, 4 H).

[1111]

(2)3-{[(4-{[cyclohexyl(3,5-dimethyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclohexyl(3,5-dimethyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (471 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 3 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (407 mg, 92%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.37 (m, 5 H), 1.47 - 1.58 (m, 1 H), 1.60 - 1.97 (m, 4 H), 2.02 - 2.14 (m, 1 H), 2.23 (s, 3 H), 2.42 (s, 3 H), 2.62 - 2.73 (m, 2 H), 3.04 (s, 3 H), 3.70 (t, J=6.4 Hz, 2 H), 4.37 (d, J=8.0 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 7.00 - 7.06 (m, 1 H), 7.19 - 7.28 (m, 4 H).

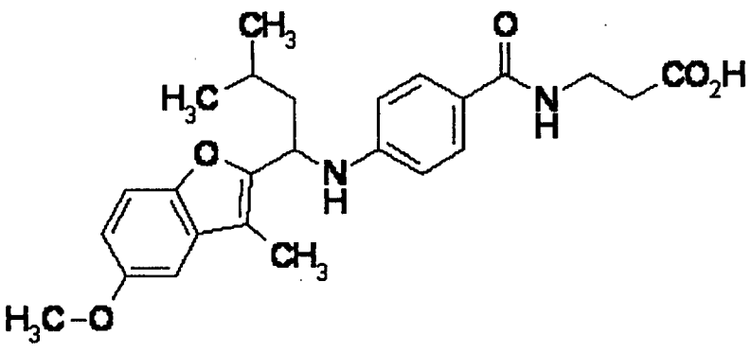
[1112]

Example A92

3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-3-

methylbutyl]amino}phenyl)carbonyl]amino}propanoic acid

[1113]



[1114]

(1)1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-3-methylbutan-1-ol

To a solution (40 mL) of 5-methoxy-3-methyl-1-benzofuran-2-carbaldehyde (1.91 g) synthesized in Example A27(2) in tetrahydrofuran was added a solution (15.0 mL) of 1.0M isobutylmagnesium bromide in tetrahydrofuran at 0°C, and the mixture was stirred for 1 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, tetrahydrofuran was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give the title object compound (1.53 g, 62%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 (d, J=6.6 Hz, 3 H), 0.95 (d, J=6.6 Hz, 3 H), 1.54 - 1.69 (m, 1 H), 1.74 - 1.96 (m, 3 H), 2.23 (s, 3 H), 3.85 (s, 3 H), 4.88 - 4.97 (m, 1 H), 6.86 (dd, J=8.6, 2.7 Hz, 1 H), 6.91 (d, J=2.7 Hz, 1 H), 7.30 (d, J=8.6 Hz, 1 H).

[1115]

(2)2-(1-chloro-3-methylbutyl)-5-methoxy-3-methyl-1-benzofuran

To a solution (10 mL) of 1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-3-methylbutan-1-ol (761 mg) synthesized above in toluene were added pyridine (297 µL) and thionyl chloride

(268 μL), and the mixture was stirred at room temperature for 3 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (769 mg, 94%) as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 - 0.96 (m, 3 H), 1.12 (d, J=6.8 Hz, 3 H), 1.58 - 1.75 (m, 1 H), 2.15 (d, J=7.9 Hz, 2 H), 2.24 (s, 3 H), 3.86 (s, 3 H), 5.20 (t, J=7.8 Hz, 1 H), 6.86 - 6.93 (m, 2 H), 7.34 (d, J=9.4 Hz, 1 H).

[1116]

(3) ethyl 3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl]amino}propanoate

A mixture of 2-(1-chloro-3-methylbutyl)-5-methoxy-3-methyl-1-benzofuran (380 mg) synthesized above, ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (350 mg) synthesized in Example 1(2), sodium iodide (443 mg), sodium carbonate (314 mg) and N,N-dimethylformamide (10 mL) was stirred at 80°C for 5 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% ethyl acetate/hexane) to give the title object compound (266 mg, 40%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.8 Hz, 3 H), 1.00 (d, J=6.8 Hz, 3 H), 1.20 - 1.30 (m, 3 H), 1.49 - 1.64 (m, 1 H), 1.79 - 1.91 (m, 2 H), 2.26 (s, 3 H), 2.59 (t, J=5.9 Hz, 2 H), 3.62 - 3.71 (m, 2 H), 3.83 (s, 3 H), 4.07 - 4.21 (m, 2 H), 4.30 - 4.44 (m, 1 H), 4.70 (t, J=7.4 Hz, 1 H), 6.56 - 6.63 (m, 3 H), 6.80 - 6.85 (m, 1 H), 6.88 (d, J=2.3 Hz, 1 H), 7.25 (d, J=8.7 Hz, 1 H), 7.56 (d, J=8.7 Hz, 2 H).

[1117]

(4)3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-3-

methylbutyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl]amino}propanoate (266 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (216 mg, 86%) as a white solid.

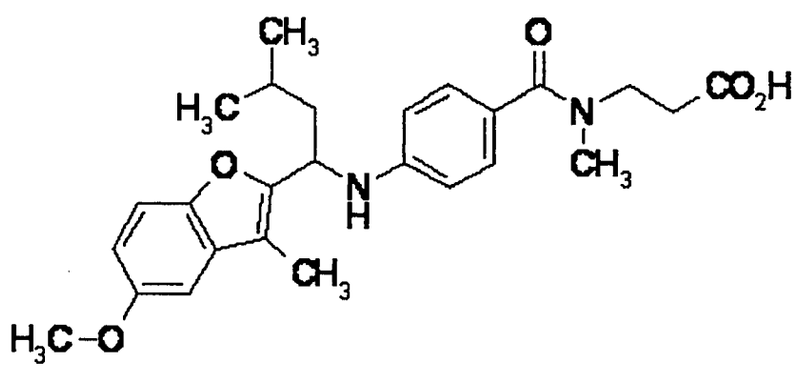
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 (d, J=6.4 Hz, 3 H), 0.99 (d, J=6.4 Hz, 3 H), 1.48 - 1.64 (m, 1 H), 1.76 - 1.93 (m, 2 H), 2.25 (s, 3 H), 2.63 (t, J=5.7 Hz, 2 H), 3.59 - 3.69 (m, 2 H), 3.83 (s, 3 H), 4.70 (t, J=7.4 Hz, 1 H), 6.54 - 6.65 (m, 3 H), 6.78 - 6.85 (m, 1 H), 6.87 (d, J=2.7 Hz, 1 H), 7.20 - 7.30 (m, 1 H), 7.53 (d, J=8.7 Hz, 2 H).

[1118]

Example A93

3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1119]



[1120]

(1) ethyl 3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl](methyl)amino}propanoate

476

A mixture of 2-(1-chloro-3-methylbutyl)-5-methoxy-3-methyl-1-benzofuran (380 mg) synthesized in Example A92(2), ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (370 mg) synthesized in Example 2(2), sodium iodide (443 mg), sodium carbonate (314 mg) and N,N-dimethylformamide (10 mL) was stirred at 80°C for 5 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60% ethyl acetate/hexane) to give the title object compound (350 mg, 51%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.4 Hz, 3 H), 1.00 (d, J=6.8 Hz, 3 H), 1.19 - 1.30 (m, 3 H), 1.49 - 1.64 (m, 1 H), 1.80 - 1.89 (m, 2 H), 2.26 (s, 3 H), 2.61 (t, J=7.0 Hz, 2 H), 3.01 (s, 3 H), 3.71 (t, J=7.0 Hz, 2 H), 3.84 (s, 3 H), 4.07 - 4.17 (m, 2 H), 4.68 (t, J=7.4 Hz, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 6.80 - 6.86 (m, 1 H), 6.88 (d, J=2.3 Hz, 1 H), 7.23 (d, J=8.7 Hz, 2 H), 7.26 (d, J=8.7 Hz, 1 H).

[1121]

(2)3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl](methyl)amino}propanoate (350 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (308 mg, 94%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.4 Hz, 3 H), 1.00 (d, J=6.4 Hz, 3 H), 1.48 - 1.65 (m, 1 H), 1.81 - 1.89 (m, 2 H),

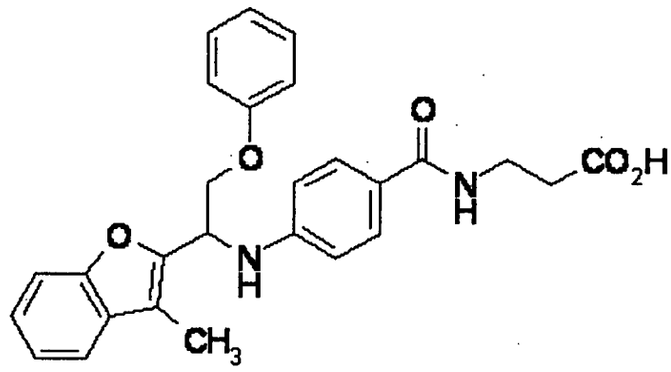
2.26 (s, 3 H), 2.65 - 2.75 (m, 2 H), 3.05 (s, 3 H), 3.71 (t, J=6.4 Hz, 2 H), 3.84 (s, 3 H), 4.69 (t, J=7.4 Hz, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 6.80 - 6.86 (m, 1 H), 6.88 (d, J=2.3 Hz, 1 H), 7.23 - 7.30 (m, 3 H).

[1122]

Example A94

3-{[(4-{[1-(3-methyl-1-benzofuran-2-yl)-2-phenoxyethyl]amino}phenyl)carbonyl]amino}propanoic acid

[1123]



[1124]

(1)1-(3-methyl-1-benzofuran-2-yl)-2-phenoxyethanone

To a mixture of 2-bromo-1-(3-methyl-1-benzofuran-2-yl)ethanone (1.00 g), phenol (446 mg) and N,N-dimethylformamide (20 mL) was added potassium carbonate (655 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% ethyl acetate/hexane) to give the title object compound (697 mg, 66%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.65 (s, 3 H), 5.36 (s, 2 H), 6.81 - 6.86 (m, 1 H), 6.98 - 7.06 (m, 2 H), 7.20 - 7.39 (m, 3 H), 7.51 - 7.57 (m, 2 H), 7.67 - 7.73 (m, 1 H).

[1125]

(2) methyl 4-{[1-(3-methyl-1-benzofuran-2-yl)-2-phenoxyethyl]amino}benzoate

To a mixture of 1-(3-methyl-1-benzofuran-2-yl)-2-phenoxyethanone (697 mg) synthesized above, methyl 4-aminobenzoate (399 mg), triethylamine (2.93 mL) and methylene chloride (10 mL) was added titanium (IV) chloride (344 μL) at 0°C under argon atmosphere, and the mixture was stirred overnight at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, methylene chloride was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (20 mL) of the obtained oil in tetrahydrofuran were added acetic acid (2 mL) and sodium cyanoborohydride (329 mg), and the mixture was stirred at room temperature for 15 min. Trifluoroacetic acid (2 mL) was added to the reaction mixture, and the mixture was further stirred at room temperature for 3 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% ethyl acetate/hexane) to give the title object compound (279 mg, 27%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.29 (s, 3 H), 3.83 (s, 3 H), 4.32 - 4.44 (m, 2 H), 4.91 (d, J=6.6 Hz, 1 H), 5.08 - 5.16 (m, 1 H), 6.66 (d, J=8.9 Hz, 1 H), 6.81 - 6.99 (m, 3 H), 7.18 - 7.31 (m, 4 H), 7.38 - 7.48 (m, 2 H), 7.84 (d, J=8.9 Hz, 2 H).

[1126]

(3)4-{[1-(3-methyl-1-benzofuran-2-yl)-2-phenoxyethyl]amino}benzoic acid

To a mixture of methyl 4-{[1-(3-methyl-1-benzofuran-2-yl)-2-phenoxyethyl]amino}benzoate (279 mg) synthesized above,

tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (5.00 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (5.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (220 mg, 82%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.30 (s, 3 H), 4.32 - 4.46 (m, 2 H), 4.92 - 5.03 (m, 1 H), 5.09 - 5.20 (m, 1 H), 6.69 (d, J=9.1 Hz, 2 H), 6.90 (d, J=7.6 Hz, 2 H), 6.93 - 7.01 (m, 1 H), 7.19 - 7.34 (m, 4 H), 7.38 - 7.51 (m, 2 H), 7.90 (d, J=8.7 Hz, 2 H).

[1127]

(4) ethyl 3-{[(4-{[1-(3-methyl-1-benzofuran-2-yl)-2-phenoxyethyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[1-(3-methyl-1-benzofuran-2-yl)-2-phenoxyethyl]amino}benzoic acid (100 mg) synthesized above, β-alanine ethyl ester hydrochloride (59.4 mg), 1-hydroxybenzotriazole monohydrate (59.3 mg), triethylamine (72 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (74.2 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (45% ethyl acetate/hexane) to give the title object compound (63.0 mg, 50%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.25 (t, J=7.2 Hz, 3 H), 2.29 (s, 3 H), 2.59 (t, J=5.8 Hz, 2 H), 3.62 - 3.72 (m, 2 H), 4.14 (q, J=7.2 Hz, 2 H), 4.31 - 4.44 (m, 2 H), 4.78 - 4.88 (m, 1 H), 5.06 - 5.15 (m, 1 H), 6.60 - 6.71 (m, 3 H), 6.89 (dd, J=8.8, 1.0 Hz, 2 H), 6.93 - 7.00 (m, 1 H), 7.18 - 7.31 (m, 4 H), 7.38 - 7.49 (m, 2 H), 7.59 (d, J=8.9 Hz, 2 H).

[1128]

(5)3-{[(4-{[1-(3-methyl-1-benzofuran-2-yl)-2-phenoxyethyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[1-(3-methyl-1-benzofuran-2-yl)-2-phenoxyethyl]amino}phenyl)carbonyl]amino}propanoate (63.0 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (57.5 mg, 97%) as a pale-brown solid.

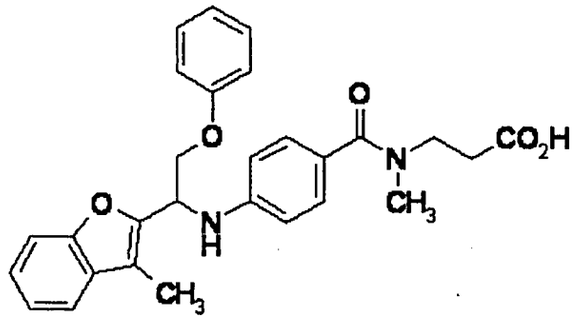
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.29 (s, 3 H), 2.68 (t, J=5.9 Hz, 2 H), 3.63 - 3.72 (m, 2 H), 4.32 - 4.44 (m, 2 H), 5.10 (t, J=6.1 Hz, 1 H), 6.58 (t, J=5.7 Hz, 1 H), 6.67 (d, J=8.7 Hz, 2 H), 6.87 - 6.92 (m, 2 H), 6.93 - 7.00 (m, 1 H), 7.18 - 7.31 (m, 4 H), 7.38 - 7.43 (m, 1 H), 7.44 - 7.49 (m, 1 H), 7.58 (d, J=8.7 Hz, 2 H).

[1129]

Example A95

3-{methyl[(4-{[1-(3-methyl-1-benzofuran-2-yl)-2-phenoxyethyl]amino}phenyl)carbonyl]amino}propanoic acid

[1130]




[1131]

(1) ethyl 3-{methyl[(4-{[1-(3-methyl-1-benzofuran-2-yl)-2-phenoxyethyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[1-(3-methyl-1-benzofuran-2-yl)-2-phenoxyethyl]amino}benzoic acid (100 mg) synthesized in Example A94(3), ethyl 3-(methylamino)propanoate (50.8 mg), 1-hydroxybenzotriazole monohydrate (59.3 mg), triethylamine (54 µL) and N,N-dimethylformamide (10 mL) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (74.2 mg) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% ethyl acetate/hexane) to give the title object compound (82.5 mg, 64%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.23 (t, J=7.2 Hz, 3 H), 2.29 (s, 3 H), 2.57 - 2.67 (m, 2 H), 3.02 (s, 3 H), 3.72 (t, J=7.1 Hz, 2 H), 4.12 (q, J=7.2 Hz, 2 H), 4.30 - 4.44 (m, 2 H), 5.08 (t, J=6.0 Hz, 1 H), 6.66 (d, J=8.7 Hz, 2 H), 6.90 (dd, J=8.7, 0.9 Hz, 2 H), 6.93 - 7.01 (m, 1 H), 7.19 - 7.32 (m, 6 H), 7.38 - 7.50 (m, 2 H).

[1132]

(2)3-{methyl[(4-{[1-(3-methyl-1-benzofuran-2-yl)-2-phenoxyethyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{methyl[(4-{[1-(3-methyl-1-benzofuran-2-yl)-2-phenoxyethyl]amino}phenyl)carbonyl]amino}propanoate (82.5 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (54.8 mg, 70%) as a white solid.

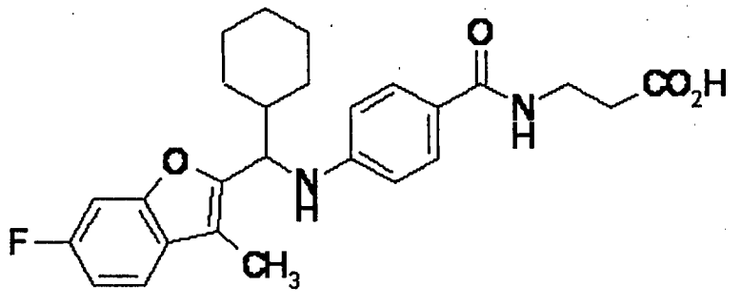
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.29 (s, 3 H), 2.61 - 2.72 (m, 2 H), 3.04 (s, 3 H), 3.71 (t, J=6.6 Hz, 2 H), 4.30 - 4.42 (m, 2 H), 5.08 (t, J=6.1 Hz, 1 H), 6.66 (d, J=8.7 Hz, 2 H), 6.86 - 6.92 (m, 2 H), 6.92 - 7.00 (m, 1 H), 7.18 - 7.31 (m, 6 H), 7.38 - 7.43 (m, 1 H), 7.44 - 7.49 (m, 1 H).

[1133]

Example A96

3-{[(4-{[cyclohexyl(6-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1134]




[1135]

(1) 6-fluoro-N-methoxy-N,3-dimethyl-1-benzofuran-2-carboxamide

To a solution (50 mL) of 1-(4-fluoro-2-hydroxyphenyl)ethanone (5.00 g) in N,N-dimethylformamide were added 2-chloro-N-methoxy-N-methylacetamide (4.90 g), sodium iodide (9.71 g) and potassium carbonate (8.96 g), and the mixture was stirred overnight at 80°C. The reaction mixture was cooled to room temperature, the insoluble material was filtered off. 1,8-diazabicyclo[5.4.0]undec-7-ene (4.85 mL) was added to the filtrate, and the mixture was stirred at 120°C for 2 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% ethyl acetate/hexane) to give the title object compound (3.65 g, 47%) as a pale-brown oil

$^1$H NMR (300 MHz, $CDCl_3$) δ 2.50 (s, 3 H), 3.38 (s, 3 H), 3.87 (s,

3 H), 7.01 - 7.11 (m, 1 H), 7.18 (dd, J=8.8, 1.9 Hz, 1 H), 7.54 (dd, J=8.8, 5.5 Hz, 1 H).

[1136]

(2) 6-fluoro-3-methyl-1-benzofuran-2-carbaldehyde

To a solution (50 mL) of 6-fluoro-N-methoxy-N,3-dimethyl-1-benzofuran-2-carboxamide (3.65 g) synthesized above in tetrahydrofuran was added lithium aluminum hydride (292 mg) at 0°C, and the mixture was stirred for 1 hr. Water (300 µL) was added to quench the reaction, 1N aqueous sodium hydroxide solution (600 µL) was added, and the mixture was stirred at room temperature for 1 hr. The resulting insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give the title object compound (1.88 g, 69%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.62 (s, 3 H), 7.07 - 7.15 (m, 1 H), 7.22 - 7.28 (m, 1 H), 7.65 (dd, J=8.8, 5.4 Hz, 1 H), 9.99 (s, 1 H).

[1137]

(3) cyclohexyl(6-fluoro-3-methyl-1-benzofuran-2-yl)methanol

To a solution (20 mL) of 6-fluoro-3-methyl-1-benzofuran-2-carbaldehyde (940 mg) synthesized above in tetrahydrofuran was added a 1.0M solution (7.92 mL) of cyclohexylmagnesium bromide in tetrahydrofuran at 0°C, and the mixture was stirred for 1 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, tetrahydrofuran was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15% ethyl acetate/hexane) to give the title object compound (931 mg, 67%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 - 1.00 (m, 1 H), 1.00 - 1.44 (m, 5 H), 1.60 - 1.71 (m, 2 H), 1.76 - 1.99 (m, 3 H), 2.10 - 2.23 (m, 4 H), 4.50 (dd, J=8.3, 6.1 Hz, 1 H), 6.94 - 7.02 (m,

1 H), 7.10 - 7.17 (m, 1 H), 7.34 - 7.40 (m, 1 H).

[1138]

(4)2-[chloro(cyclohexyl)methyl]-6-fluoro-3-methyl-1-benzofuran

To a solution (20 mL) of cyclohexyl(6-fluoro-3-methyl-1-benzofuran-2-yl)methanol (931 mg) synthesized above in toluene was added thionyl chloride (311 μL), and the mixture was stirred at 100°C for 1 hr. The reaction mixture was poured into ice-cooled saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (945 mg, 95%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.82 - 0.98 (m, 1 H), 0.99 - 1.52 (m, 5 H), 1.60 - 1.72 (m, 2 H), 1.76 - 1.89 (m, 1 H), 2.11 - 2.25 (m, 4 H), 2.26 - 2.39 (m, 1 H), 4.79 (d, J=9.6 Hz, 1 H), 6.96 - 7.04 (m, 1 H), 7.15 - 7.20 (m, 1 H), 7.35 - 7.41 (m, 1 H).

[1139]

(5)4-{[cyclohexyl(6-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}benzoic acid

To a mixture of 2-[chloro(cyclohexyl)methyl]-6-fluoro-3-methyl-1-benzofuran (945 mg) synthesized above, methyl 4-aminobenzoate (508 mg), sodium iodide (1.01 g) and N,N-dimethylformamide (10 mL) was added sodium carbonate (712 mg), and the mixture was stirred at 80°C overnight. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give a yellow solid. To a mixture of the obtained solid, tetrahydrofuran (20 mL) and ethanol (20 mL) was added 1N aqueous sodium hydroxide solution (10.0 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved

in water (40 mL), and 1N hydrochloric acid (10.0 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (722 mg, 56%) as a brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.38 (m, 5 H), 1.46 - 1.57 (m, 1 H), 1.61 - 1.98 (m, 4 H), 2.02 - 2.13 (m, 1 H), 2.25 (s, 3 H), 4.40 (d, J=7.9 Hz, 1 H), 4.51 - 4.74 (m, 1 H), 6.57 (d, J=8.8 Hz, 2 H), 6.91 - 7.00 (m, 1 H), 7.06 - 7.12 (m, 1 H), 7.29 - 7.36 (m, 1 H), 7.85 (d, J=8.8 Hz, 2 H).

[1140]

(6) ethyl 3-{[(4-{[cyclohexyl(6-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[cyclohexyl(6-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}benzoic acid (350 mg) synthesized above, β-alanine ethyl ester hydrochloride (212 mg), 1-hydroxybenzotriazole monohydrate (211 mg), triethylamine (383 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (265 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% ethyl acetate/hexane) to give the title object compound (403 mg, 91%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.39 (m, 8 H), 1.46 - 1.57 (m, 1 H), 1.62 - 1.97 (m, 4 H), 2.03 - 2.14 (m, 1 H), 2.24 (s, 3 H), 2.58 (t, J=5.9 Hz, 2 H), 3.61 - 3.70 (m, 2 H), 4.14 (q, J=7.2 Hz, 2 H), 4.32 - 4.47 (m, 2 H), 6.54 - 6.63 (m, 3 H), 6.90 - 7.00 (m, 1 H), 7.05 - 7.12 (m, 1 H), 7.28 - 7.35 (m, 1 H), 7.55 (d, J=8.9 Hz, 2 H).

[1141]

(7)3-{[(4-{[cyclohexyl(6-fluoro-3-methyl-1-benzofuran-2-

yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclohexyl(6-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate (403 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 3 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (355 mg, 93%) as a white solid.

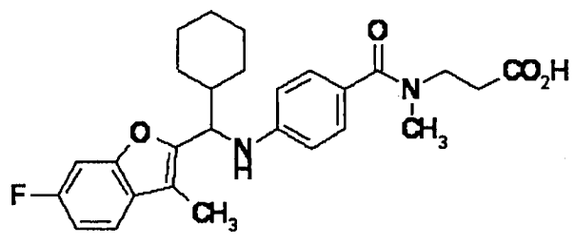
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.37 (m, 5 H), 1.44 - 1.56 (m, 1 H), 1.60 - 1.96 (m, 4 H), 2.00 - 2.12 (m, 1 H), 2.22 (s, 3 H), 2.53 - 2.66 (m, 2 H), 3.54 - 3.67 (m, 2 H), 4.35 (d, J=8.3 Hz, 1 H), 6.48 - 6.64 (m, 3 H), 6.89 - 6.99 (m, 1 H), 7.03 - 7.11 (m, 1 H), 7.27 - 7.34 (m, 1 H), 7.52 (d, J=8.7 Hz, 2 H).

[1142]

Example A97

3-{[(4-{[cyclohexyl(6-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1143]



[1144]

(1) ethyl 3-{[(4-{[cyclohexyl(6-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[cyclohexyl(6-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}benzoic acid (350 mg) synthesized in Example A96(5), ethyl 3-(methylamino)propanoate (181 mg),

1-hydroxybenzotriazole monohydrate (211 mg), triethylamine (383 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (265 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% ethyl acetate/hexane) to give the title object compound (432 mg, 95%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.37 (m, 8 H), 1.46 - 1.56 (m, 1 H), 1.60 - 1.96 (m, 4 H), 2.02 - 2.14 (m, 1 H), 2.23 (s, 3 H), 2.61 (t, J=6.9 Hz, 2 H), 3.01 (s, 3 H), 3.70 (t, J=6.9 Hz, 2 H), 4.07 - 4.17 (m, 2 H), 4.27 - 4.39 (m, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.91 - 7.00 (m, 1 H), 7.06 - 7.12 (m, 1 H), 7.21 (d, J=8.7 Hz, 2 H), 7.28 - 7.35 (m, 1 H).

[1145]

(2)3-{[(4-{[cyclohexyl(6-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclohexyl(6-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (432 mg) synthesized above, tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 4 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (367 mg, 90%) as a pale-red solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.37 (m, 5 H), 1.46 - 1.57 (m, 1 H), 1.61 - 1.96 (m, 4 H), 2.03 - 2.14 (m, 1 H), 2.23 (s, 3 H), 2.67 (t, J=6.4 Hz, 2 H), 3.04 (s, 3 H), 3.70 (t, J=6.4

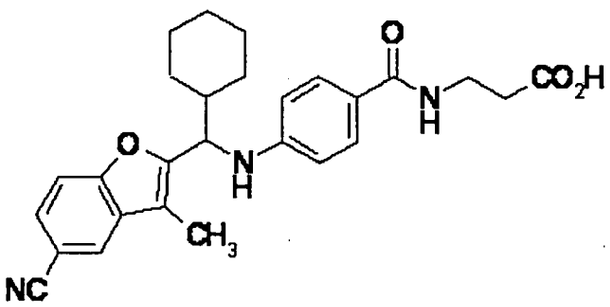
Hz, 2 H), 4.35 (d, J=8.0 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.91 - 7.00 (m, 1 H), 7.06 - 7.12 (m, 1 H), 7.21 - 7.28 (m, 2 H), 7.29 - 7.36 (m, 1 H).

[1146]

Example A98

3-{[(4-{[(5-cyano-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1147]



[1148]

(1)methyl 5-bromo-3-methyl-1-benzofuran-2-carboxylate

To a solution (100 mL) of 1-(5-bromo-2-hydroxyphenyl)ethanone (10.0 g) in N,N-dimethylformamide were added methyl bromoacetate (4.85 mL) and potassium carbonate (12.9 g), and the mixture was stirred overnight at room temperature. The insoluble material was filtered off, 1,8-diazabicyclo[5.4.0]undec-7-ene (6.95 mL) was added to the filtrate, and the mixture was stirred at 120°C for 2 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% ethyl acetate/hexane) to give the title object compound (6.06 g, 48%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.56 (s, 3 H), 3.99 (s, 3 H), 7.39 - 7.44 (m, 1 H), 7.51 - 7.56 (m, 1 H), 7.76 (d, J=1.9 Hz,

1 H).

[1149]

(2) methyl 5-cyano-3-methyl-1-benzofuran-2-carboxylate

To a mixture of methyl 5-bromo-3-methyl-1-benzofuran-2-carboxylate (6.06 g) synthesized above, zinc cyanide (2.64 g) and N,N-dimethylformamide (60 mL) was added tetrakis(triphenylphosphine)palladium (0) (1.31 g), and the mixture was deaerated and stirred under argon atmosphere at 80°C overnight. Water was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title object compound (4.20 g, 87%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.61 (s, 3 H), 4.01 (s, 3 H), 7.61 - 7.66 (m, 1 H), 7.69 - 7.74 (m, 1 H), 8.00 (d, J=0.9 Hz, 1 H).

[1150]

(3)5-cyano-3-methyl-1-benzofuran-2-carboxylic acid

To a mixture of methyl 5-cyano-3-methyl-1-benzofuran-2-carboxylate (4.20 g) synthesized above, tetrahydrofuran (80 mL), water (20 mL) and methanol (20 mL) was added lithium hydroxide monohydrate (1.64 g), and the mixture was stirred overnight at room temperature, and concentrated under reduced pressure. 1N Hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title object compound (3.58 g, 91%) as a pale-brown solid.

$^1$H NMR (300 MHz, DMSO-d6) δ ppm 2.55 (s, 3 H), 7.85 - 7.89 (m, 1 H), 7.91 - 7.95 (m, 1 H), 8.44 - 8.47 (m, 1 H), 13.76 (br s, 1 H).

[1151]

(4)2-formyl-3-methyl-1-benzofuran-5-carbonitrile

490

To 5-cyano-3-methyl-1-benzofuran-2-carboxylic acid (2.58 g) synthesized above in tetrahydrofuran (30 mL) were added oxalyl chloride (1.32 mL) and several drops of N,N-dimethylformamide, and the mixture was stirred at room temperature for 5 hr. The reaction mixture was concentrated under reduced pressure, and the residue was washed with diisopropyl ether to give a pale-brown solid. To a solution (50 mL) of the obtained solid in tetrahydrofuran was added a 1.1M solution (12.0 mL) of lithium tri(isobutoxy)aluminum hydride in tetrahydrofuran at -78°C, and the mixture was stirred at -78°C for 1.5 hr then at 0°C for 3 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a pale-brown solid. To a solution (40 mL) of the obtained solid in tetrahydrofuran was added active manganese dioxide (10.0 g), and the mixture was stirred at 50°C overnight. Manganese dioxide was filtered off, and the filtrate was concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title object compound (1.49 g, 63%) as a white solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.65 (s, 3 H), 7.65 (d, J=8.7 Hz, 1 H), 7.77 (dd, J=8.7, 1.5 Hz, 1 H), 8.05 - 8.08 (m, 1 H), 10.08 (s, 1 H).

[1152]

(5)2-[cyclohexyl(hydroxy)methyl]-3-methyl-1-benzofuran-5-carbonitrile

To a solution (30 mL) of 2-formyl-3-methyl-1-benzofuran-5-carbonitrile (1.49 g) synthesized above in tetrahydrofuran was added a 1.0M solution (12.1 mL) of cyclohexylmagnesium bromide in tetrahydrofuran at 0°C, and the mixture was stirred for 1 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and

concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% ethyl acetate/hexane), and then purified by NH silica gel column chromatography (ethyl acetate) to give the title object compound (922 mg, 43%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 - 1.43 (m, 6 H), 1.48 - 1.99 (m, 5 H), 2.03 - 2.19 (m, 1 H), 2.24 (s, 3 H), 4.56 (dd, J=8.4, 5.4 Hz, 1 H), 7.47 - 7.51 (m, 1 H), 7.52 - 7.57 (m, 1 H), 7.78 - 7.81 (m, 1 H).

[1153]

(6)2-[chloro(cyclohexyl)methyl]-3-methyl-1-benzofuran-5-carbonitrile

To a solution (10 mL) of 2-[cyclohexyl(hydroxy)methyl]-3-methyl-1-benzofuran-5-carbonitrile (922 mg) synthesized above in toluene was added thionyl chloride (374 μL), and the mixture was stirred at 100°C for 1 hr. The reaction mixture was poured into ice-cooled saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (868 mg, 88%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 - 1.55 (m, 6 H), 1.62 - 1.74 (m, 2 H), 1.79 - 1.90 (m, 1 H), 2.10 - 2.22 (m, 1 H), 2.26 (s, 3 H), 2.28 - 2.39 (m, 1 H), 4.80 (d, J=9.6 Hz, 1 H), 7.51 - 7.55 (m, 1 H), 7.56 - 7.61 (m, 1 H), 7.81 - 7.83 (m, 1 H).

[1154]

(7)4-{[(5-cyano-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}benzoic acid

To a mixture of 2-[chloro(cyclohexyl)methyl]-3-methyl-1-benzofuran-5-carbonitrile (868 mg) synthesized above, methyl 4-aminobenzoate (546 mg), sodium iodide (902 mg) and N,N-dimethylformamide (10 mL) was added sodium carbonate (638 mg), and the mixture was stirred at 80°C overnight. 1N Hydrochloric acid was added to quench the reaction, and the mixture was

extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30% ethyl acetate/hexane) to give a pale-brown solid. To a mixture of the obtained solid, tetrahydrofuran (20 mL), water (8 mL) and ethanol (10 mL) was added 1N lithium hydroxide aqueous solution (3.38 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (40 mL), and 1N hydrochloric acid (3.50 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (621 mg, 53%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 1.41 (m, 5 H), 1.44 - 1.56 (m, 1 H), 1.62 - 2.01 (m, 4 H), 2.03 - 2.14 (m, 1 H), 2.28 (s, 3 H), 4.40 - 4.51 (m, 1 H), 4.52 - 4.67 (m, 1 H), 6.56 (d, J=8.8 Hz, 2 H), 7.41 - 7.46 (m, 1 H), 7.49 - 7.54 (m, 1 H), 7.75 - 7.77 (m, 1 H), 7.85 (d, J=8.8 Hz, 2 H).

[1155]

(8) ethyl 3-{[(4-{[(5-cyano-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[(5-cyano-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}benzoic acid (250 mg) synthesized above, β-alanine ethyl ester hydrochloride (148 mg), 1-hydroxybenzotriazole monohydrate (148 mg), triethylamine (269 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (185 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% ethyl acetate/hexane) to give the title object compound (195 mg,

62%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.38 (m, 8 H), 1.45 - 1.63 (m, 3 H), 1.63 - 1.99 (m, 2 H), 2.03 - 2.15 (m, 1 H), 2.27 (s, 3 H), 2.54 - 2.61 (m, 2 H), 3.61 - 3.70 (m, 2 H), 4.14 (q, J=7.2 Hz, 2 H), 4.39 - 4.46 (m, 1 H), 6.53 - 6.64 (m, 3 H), 7.41 - 7.45 (m, 1 H), 7.48 - 7.53 (m, 1 H), 7.55 (d, J=8.7 Hz, 2 H), 7.76 (d, J=1.5 Hz, 1 H).

[1156]

(9)3-{[(4-{[(5-cyano-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[(5-cyano-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoate (195 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N lithium hydroxide aqueous solution (800 µL), and the mixture was stirred at room temperature for 5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (800 µL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (168 mg, 92%) as a white solid.

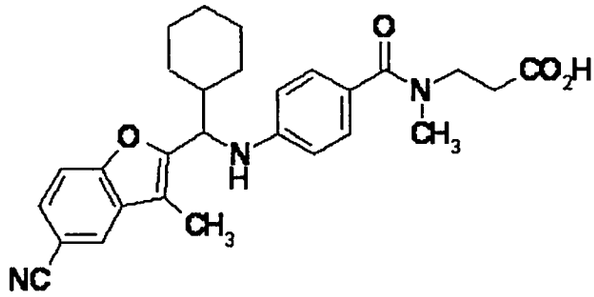
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.37 (m, 5 H), 1.43 - 1.54 (m, 1 H), 1.62 - 1.98 (m, 4 H), 2.03 - 2.14 (m, 1 H), 2.26 (s, 3 H), 2.57 - 2.67 (m, 2 H), 3.54 - 3.70 (m, 2 H), 4.42 (d, J=8.1 Hz, 1 H), 6.51 - 6.65 (m, 3 H), 7.39 - 7.44 (m, 1 H), 7.45 - 7.56 (m, 3 H), 7.74 (d, J=1.1 Hz, 1 H).

[1157]

Example A99

3-{[(4-{[(5-cyano-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[1158]



[1159]

(1) ethyl 3-{[(4-{[(5-cyano-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate

To a mixture of 4-{[(5-cyano-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}benzoic acid (250 mg) synthesized in Example A98(7), ethyl 3-(methylamino)propanoate (127 mg), 1-hydroxybenzotriazole monohydrate (148 mg), triethylamine (269 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (185 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% ethyl acetate/hexane) to give the title object compound (193 mg, 60%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.38 (m, 8 H), 1.44 - 1.54 (m, 1 H), 1.62 - 1.98 (m, 4 H), 2.05 - 2.15 (m, 1 H), 2.27 (s, 3 H), 2.55 - 2.66 (m, 2 H), 3.00 (s, 3 H), 3.70 (t, J=7.1 Hz, 2 H), 4.11 (q, J=7.0 Hz, 2 H), 4.26 - 4.33 (m, 1 H), 4.40 (t, J=7.9 Hz, 1 H), 6.55 (d, J=8.6 Hz, 2 H), 7.21 (d, J=8.6 Hz, 2 H), 7.40 - 7.46 (m, 1 H), 7.48 - 7.54 (m, 1 H), 7.76 (d, J=1.5 Hz, 1 H).

[1160]

(2) 3-{[(4-{[(5-cyano-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

To a mixture of ethyl 3-{[(4-{[(5-cyano-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (193 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N lithium hydroxide aqueous solution (770 μL), and the mixture was stirred at room temperature for 3 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (770 μL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (163 mg, 90%) as a white solid.

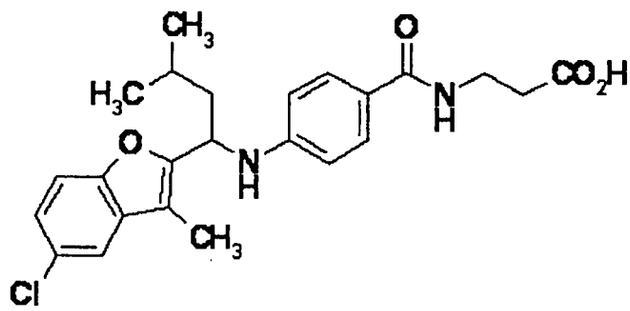
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.37 (m, 5 H), 1.44 - 1.54 (m, 1 H), 1.62 - 1.98 (m, 4 H), 2.04 - 2.15 (m, 1 H), 2.27 (s, 3 H), 2.61 - 2.70 (m, 2 H), 3.03 (s, 3 H), 3.69 (t, J=6.5 Hz, 2 H), 4.40 (d, J=7.9 Hz, 1 H), 6.55 (d, J=8.9 Hz, 2 H), 7.24 (d, J=8.9 Hz, 2 H), 7.40 - 7.46 (m, 1 H), 7.48 - 7.53 (m, 1 H), 7.76 (d, J=1.1 Hz, 1 H).

[1161]

Example A100

3-{[(4-{[1-(5-chloro-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl]amino}propanoic acid

[1162]



[1163]

(1) 1-(5-chloro-3-methyl-1-benzofuran-2-yl)-3-methylbutan-1-ol

To a solution (20 mL) of 5-chloro-3-methyl-1-benzofuran-2-carbaldehyde (1.00 g) synthesized in Example A88(2) in tetrahydrofuran was added a 1.0M solution (10.3 mL) of isobutylmagnesium bromide in tetrahydrofuran at 0°C, and the mixture was stirred for 1 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give the title object compound (650 mg, 50%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 - 0.98 (m, 6 H), 1.53 - 1.70 (m, 1 H), 1.71 - 1.97 (m, 3 H), 2.22 (s, 3 H), 4.89 - 4.98 (m, 1 H), 7.19 - 7.23 (m, 1 H), 7.31 - 7.35 (m, 1 H), 7.43 (d, J=2.2 Hz, 1 H).

[1164]

(2)5-chloro-2-(1-chloro-3-methylbutyl)-3-methyl-1-benzofuran

To a solution (10 mL) of 1-(5-chloro-3-methyl-1-benzofuran-2-yl)-3-methylbutan-1-ol (650 mg) synthesized above in toluene was added thionyl chloride (225 μL), and the mixture was stirred at 50°C for 2 hr. The reaction mixture was poured into ice-cooled saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (668 mg, 96%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 (d, J=2.5 Hz, 3 H), 0.95 (d, J=2.7 Hz, 3 H), 1.58 - 1.74 (m, 1 H), 2.06 - 2.21 (m, 2 H), 2.23 (s, 3 H), 5.17 (t, J=8.0 Hz, 1 H), 7.22 - 7.27 (m, 1 H), 7.34 - 7.38 (m, 1 H), 7.44 (d, J=2.2 Hz, 1 H).

[1165]

(3)4-{[1-(5-chloro-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}benzoic acid

To a mixture of 5-chloro-2-(1-chloro-3-methylbutyl)-3-methyl-1-benzofuran (668 mg) synthesized above, methyl 4-aminobenzoate (410 mg), sodium iodide (737 mg) and N,N-dimethylformamide (10 mL) was added sodium carbonate (521 mg) and the mixture was stirred at 80°C for 8 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15% ethyl acetate/hexane) to give a yellow oil. To a mixture of the obtained oil, tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N aqueous sodium hydroxide solution (10.0 mL), and the mixture was stirred with heating under reflux for 8 hr, and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (10.0 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (394 mg, 43%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 (d, J=6.6 Hz, 3 H), 1.01 (d, J=6.6 Hz, 3 H), 1.47 - 1.65 (m, 1 H), 1.87 (t, J=7.4 Hz, 2 H), 2.27 (s, 3 H), 4.75 (t, J=7.4 Hz, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 7.16 - 7.21 (m, 1 H), 7.27 - 7.31 (m, 1 H), 7.40 (d, J=2.1 Hz, 1 H), 7.86 (d, J=8.7 Hz, 2 H).

[1166]

(4) ethyl 3-{[(4-{[1-(5-chloro-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[1-(5-chloro-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}benzoic acid (180 mg) synthesized above, β-alanine ethyl ester hydrochloride (112 mg), 1-hydroxybenzotriazole monohydrate (111 mg), triethylamine (202 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (139 mg) and the mixture was stirred at room temperature for 2.5 days. 1N Hydrochloric acid was added to quench the reaction, and the

mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% ethyl acetate/hexane) to give the title object compound (196 mg, 86%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.3 Hz, 3 H), 1.00 (d, J=6.6 Hz, 3 H), 1.25 (t, J=7.1 Hz, 3 H), 1.48 - 1.64 (m, 1 H), 1.85 (t, J=7.3 Hz, 2 H), 2.25 (s, 3 H), 2.55 - 2.62 (m, 2 H), 3.61 - 3.69 (m, 2 H), 4.13 (q, J=7.1 Hz, 2 H), 4.30 - 4.39 (m, 1 H), 4.65 - 4.76 (m, 1 H), 6.53 - 6.65 (m, 3 H), 7.13 - 7.19 (m, 1 H), 7.23 - 7.29 (m, 1 H), 7.38 (d, J=2.2 Hz, 1 H), 7.55 (d, J=8.8 Hz, 2 H).

[1167]

(5)3-{[(4-{[1-(5-chloro-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[1-(5-chloro-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl]amino}propanoate (196 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.50 mL), and the mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.50 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (170 mg, 92%) as a white solid.

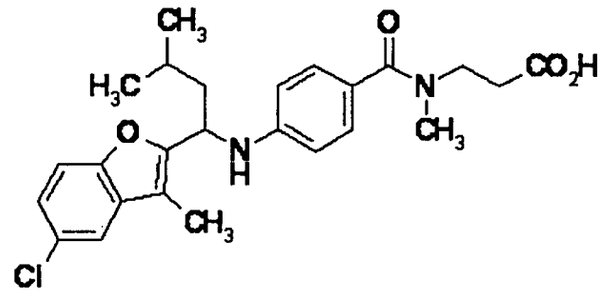
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.8 Hz, 3 H), 1.00 (d, J=6.4 Hz, 3 H), 1.48 - 1.63 (m, 1 H), 1.85 (t, J=7.5 Hz, 2 H), 2.24 (s, 3 H), 2.64 (t, J=5.9 Hz, 2 H), 3.60 - 3.69 (m, 2 H), 4.70 (t, J=7.5 Hz, 1 H), 6.57 (d, J=8.7 Hz, 2 H), 6.62 (t, J=6.1 Hz, 1 H), 7.14 - 7.19 (m, 1 H), 7.24 - 7.29 (m, 1 H), 7.38 (d, J=1.9 Hz, 1 H), 7.54 (d, J=8.7 Hz, 2 H).

[1168]

Example A101

3-{[(4-{[1-(5-chloro-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1169]



[1170]

(1) ethyl 3-{[(4-{[1-(5-chloro-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[1-(5-chloro-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}benzoic acid (180 mg) synthesized in Example A100(3), ethyl 3-(methylamino)propanoate (95.2 mg), 1-hydroxybenzotriazole monohydrate (111 mg), triethylamine (202 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (139 mg), and the mixture was stirred at room temperature for 2.5 days. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (55% ethyl acetate/hexane) to give the title object compound (199 mg, 85%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.6 Hz, 3 H), 1.00 (d, J=6.6 Hz, 3 H), 1.23 (t, J=7.1 Hz, 3 H), 1.49 - 1.64 (m, 1 H), 1.84 (t, J=7.3 Hz, 2 H), 2.25 (s, 3 H), 2.56 - 2.67 (m, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.0 Hz, 2 H), 4.06 - 4.17 (m, 2 H), 4.19 - 4.29 (m, 1 H), 4.63 - 4.73 (m, 1 H), 6.56 (d, J=8.5 Hz, 2 H), 7.14 - 7.19 (m, 1 H), 7.22 (d, J=8.5 Hz, 2 H), 7.25 -

7.29 (m, 1 H), 7.38 (d, J=2.2 Hz, 1 H).

[1171]

(2)3-{[(4-{[1-(5-chloro-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[1-(5-chloro-3-methyl-1-benzofuran-2-yl)-3-methylbutyl]amino}phenyl)carbonyl](methyl)amino}propanoate (199 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.50 mL), and the mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.50 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (174 mg, 93%) as a white solid.

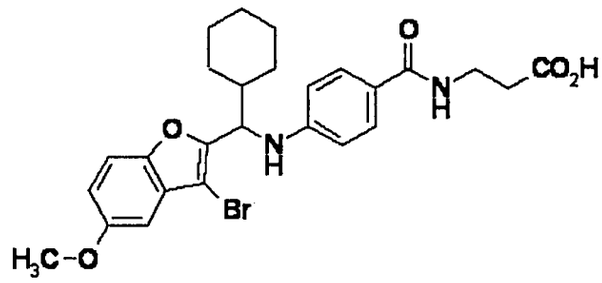
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 (d, J=6.8 Hz, 3 H), 1.00 (d, J=6.8 Hz, 3 H), 1.48 - 1.64 (m, 1 H), 1.85 (t, J=7.2 Hz, 2 H), 2.25 (s, 3 H), 2.67 (t, J=6.3 Hz, 2 H), 3.04 (s, 3 H), 3.71 (t, J=6.3 Hz, 2 H), 4.69 (t, J=7.6 Hz, 1 H), 6.57 (d, J=8.7 Hz, 2 H), 7.15 - 7.20 (m, 1 H), 7.22 - 7.31 (m, 3 H), 7.39 (d, J=1.9 Hz, 1 H).

[1172]

Example A102

3-{[(4-{[(3-bromo-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1173]




[1174]

(1)N,5-dimethoxy-N-methyl-1-benzofuran-2-carboxamide

To a solution (100 mL) of 2-hydroxy-5-methoxybenzaldehyde (10.0 g) in N,N-dimethylformamide were added 2-chloro-N-methoxy-N-methylacetamide (12.1 g), sodium iodide (24.0 g) and potassium carbonate (22.1 g), and the mixture was stirred at 50°C overnight. The reaction mixture was cooled to room temperature, and insoluble material was filtered off. To the filtrate was added 1,8-diazabicyclo[5.4.0]undec-7-ene (9.82 mL), and the mixture was stirred at 120°C for 2 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (40% ethyl acetate/hexane) to give the title object compound (9.42 g, 61%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.42 (s, 3 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 7.01 - 7.06 (m, 1 H), 7.07 - 7.09 (m, 1 H), 7.43 - 7.45 (m, 1 H), 7.46 - 7.51 (m, 1 H).

[1175]

(2)3-bromo-N,5-dimethoxy-N-methyl-1-benzofuran-2-carboxamide

To a solution (100 mL) of N,5-dimethoxy-N-methyl-1-benzofuran-2-carboxamide (9.24 g) synthesized above in acetic acid was added dropwise bromine (2.21 mL), and the mixture was stirred overnight at room temperature. The resulting precipitate was collected by filtration and washed with diisopropyl ether to give the title object compound (9.48 g, 77%) as an orange solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.43 (s, 3 H), 3.85 (s, 3 H), 3.95 (s, 3 H), 7.09 (d, J=9.0 Hz, 1 H), 7.46 - 7.54 (m, 2 H).

[1176]

(3)3-bromo-5-methoxy-1-benzofuran-2-carbaldehyde

To a solution (40 mL) of 3-bromo-N,5-dimethoxy-N-methyl-1-benzofuran-2-carboxamide (4.00 g) synthesized above in tetrahydrofuran was added lithium aluminum hydride (241 mg) at

0°C, and the mixture was stirred for 1 hr. Lithium aluminum hydride (241 mg) was additionally added, and the mixture was stirred at 0°C for 1 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give the title object compound (880 mg, 27%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.96 (s, 3 H), 7.17 (d, J=9.1 Hz, 1 H), 7.48 - 7.53 (m, 1 H), 7.55 - 7.56 (m, 1 H), 9.85 (s, 1 H).

[1177]

(4)(3-bromo-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methanol

To a solution (50 mL) of 3-bromo-5-methoxy-1-benzofuran-2-carbaldehyde (2.26 g) synthesized above in tetrahydrofuran was added a 1.0M solution (13.3 mL) of cyclohexylmagnesium bromide in tetrahydrofuran at -78°C, and the mixture was stirred at -78°C for 30 min then at 0°C for 1 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, tetrahydrofuran was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give the title object compound (1.82 g, 67%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.99 - 1.37 (m, 5 H), 1.49 - 1.60 (m, 1 H), 1.62 - 2.02 (m, 6 H), 3.93 (s, 3 H), 4.53 (t, J=6.0 Hz, 1 H), 6.63 (s, 1 H), 6.89 (d, J=8.8 Hz, 1 H), 7.34 (d, J=8.8 Hz, 1 H).

[1178]

(5)3-bromo-2-[chloro(cyclohexyl)methyl]-5-methoxy-1-benzofuran

To a solution (20 mL) of (3-bromo-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methanol (1.82 g) synthesized above in

toluene was added thionyl chloride (469 μL) and the mixture was stirred at 100°C for 1.5 hr. The reaction mixture was poured into ice-cooled saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (1.73 g, 90%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.98 - 1.39 (m, 5 H), 1.51 - 1.87 (m, 4 H), 2.03 - 2.21 (m, 2 H), 3.92 (s, 3 H), 4.74 (d, J=8.0 Hz, 1 H), 6.68 (s, 1 H), 6.92 (d, J=8.8 Hz, 1 H), 7.36 (d, J=8.8 Hz, 1 H).

[1179]

(6)4-{[(3-bromo-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}benzoic acid

To a mixture of 3-bromo-2-[chloro(cyclohexyl)methyl]-5-methoxy-1-benzofuran (1.73 g) synthesized above, methyl 4-aminobenzoate (878 mg), sodium iodide (1.45 g) and N,N-dimethylformamide (30 mL) was added sodium carbonate (1.03 g), and the mixture was stirred at 80°C for 8 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% ethyl acetate/hexane) to give a yellow oil. To a mixture of the obtained oil, tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N aqueous sodium hydroxide solution (10.0 mL), and the mixture was stirred with heating under reflux for 5 hr, and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (10.0 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (318 mg, 14%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 - 1.37 (m, 5 H), 1.55 - 1.86

(m, 4 H), 1.87 - 2.02 (m, 2 H), 3.90 (s, 3 H), 4.44 (d, J=6.6 Hz, 1 H), 6.56 (s, 1 H), 6.61 (d, J=8.9 Hz, 2 H), 6.87 (d, J=9.0 Hz, 1 H), 7.29 - 7.35 (m, 1 H), 7.87 (d, J=8.9 Hz, 2 H).

[1180]

(7) ethyl 3-{[(4-{[(3-bromo-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[(3-bromo-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}benzoic acid (125 mg) synthesized above, β-alanine ethyl ester hydrochloride (63.0 mg), 1-hydroxybenzotriazole monohydrate (62.9 mg), triethylamine (114 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (78.6 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% ethyl acetate/hexane) to give the title object compound (134 mg, 88%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 - 1.37 (m, 8 H), 1.54 - 1.85 (m, 4 H), 1.87 - 1.99 (m, 2 H), 2.56 - 2.61 (m, 2 H), 3.62 - 3.70 (m, 2 H), 3.90 (s, 3 H), 4.14 (q, J=7.1 Hz, 2 H), 4.36 - 4.41 (m, 2 H), 6.53 (d, J=0.8 Hz, 1 H), 6.56 - 6.64 (m, 3 H), 6.86 (d, J=8.8 Hz, 1 H), 7.29 (dd, J=8.8, 0.8 Hz, 1 H), 7.56 (d, J=8.8 Hz, 2 H).

[1181]

(8)3-{[(4-{[(3-bromo-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[(3-bromo-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoate (134 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol

(5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 2.5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (116 mg, 91%) as a pale-brown solid.

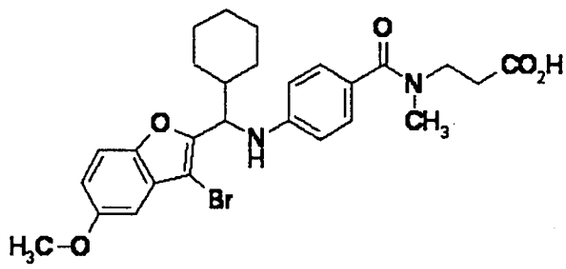
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.35 (m, 5 H), 1.53 - 1.84 (m, 4 H), 1.84 - 1.99 (m, 2 H), 2.61 (t, J=5.7 Hz, 2 H), 3.59 - 3.68 (m, 2 H), 3.89 (s, 3 H), 4.38 (d, J=6.4 Hz, 1 H), 6.52 - 6.66 (m, 4 H), 6.85 (d, J=8.9 Hz, 1 H), 7.30 (dd, J=8.9, 0.8 Hz, 1 H), 7.54 (d, J=8.7 Hz, 2 H).

[1182]

Example A103

3-{[(4-{[(3-bromo-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[1183]




[1184]

(1) ethyl 3-{[(4-{[(3-bromo-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate

To a mixture of 4-{[(3-bromo-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}benzoic acid (125 mg) synthesized in Example A102(6), ethyl 3-(methylamino)propanoate (53.8 mg), 1-hydroxybenzotriazole monohydrate (62.9 mg), triethylamine (114 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (78.6 mg),

and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (35% ethyl acetate/hexane) to give the title object compound (124 mg, 79%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 - 1.36 (m, 8 H), 1.55 - 1.85 (m, 4 H), 1.86 - 2.00 (m, 2 H), 2.62 (t, J=7.0 Hz, 2 H), 3.02 (s, 3 H), 3.72 (t, J=7.0 Hz, 2 H), 3.91 (s, 3 H), 4.12 (q, J=7.1 Hz, 2 H), 4.24 - 4.41 (m, 2 H), 6.54 - 6.55 (m, 1 H), 6.58 (d, J=8.8 Hz, 2 H), 6.86 (d, J=8.8 Hz, 1 H), 7.24 (d, J=8.8 Hz, 2 H), 7.30 (dd, J=8.8, 0.8 Hz, 1 H).

[1185]

(2)3-{[(4-{[(3-bromo-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

To a mixture of ethyl 3-{[(4-{[(3-bromo-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (124 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in ethanol (5 mL), 1N aqueous sodium hydroxide solution (500 μL) was added, and the mixture was concentrated under reduced pressure. The residue was dissolved in water (5 mL), and 1N hydrochloric acid (500 μL) was added at 0°C. The resulting

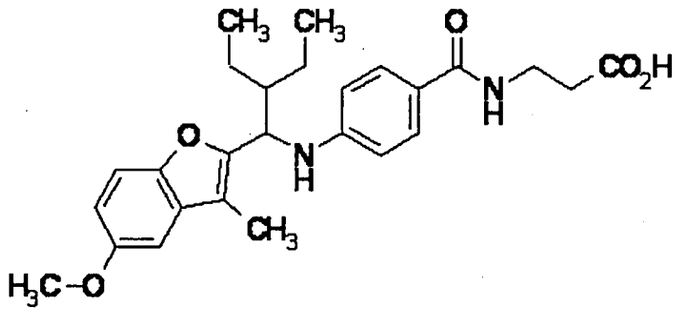
precipitate was collected by filtration to give the title object compound (107 mg, 91%) as a white solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 - 1.36 (m, 5 H), 1.53 - 1.84 (m, 4 H), 1.85 - 2.00 (m, 2 H), 2.62 - 2.75 (m, 2 H), 3.05 (s, 3 H), 3.70 (t, J=6.2 Hz, 2 H), 3.90 (s, 3 H), 4.37 (d, J=6.4 Hz, 1 H), 6.55 (s, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 6.87 (d, J=8.9 Hz, 1 H), 7.22 - 7.35 (m, 3 H).

[1186]

Example A104

3-{[(4-{[2-ethyl-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl]amino}propanoic acid

[1187]



[1188]

(1)(2-acetyl-4-methoxyphenoxy)acetic acid

To a mixture of 1-(2-hydroxy-5-methoxyphenyl)ethanone (25.0 g), methyl bromoacetate (15.5 mL) and N,N-dimethylformamide (250 mL) was added potassium carbonate (31.1 g), and the mixture was stirred overnight at room temperature. The insoluble material was filtered off, 1N hydrochloric acid was added to the filtrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a brown solid. To a mixture of the obtained solid, tetrahydrofuran (300 mL) and ethanol (300 mL) was added 1N aqueous sodium hydroxide solution (300 mL), and the mixture was stirred overnight at room temperature, and concentrated under reduced pressure. 1N Hydrochloric acid (300 mL) was

added to the residue at 0°C, and the resulting precipitate was collected by filtration to give the title object compound (34.2 g, quantitative) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.67 (s, 3 H), 3.83 (s, 3 H), 4.72 (s, 2 H), 6.92 (d, J=9.0 Hz, 1 H), 7.04 - 7.09 (m, 1 H), 7.29 (d, J=3.0 Hz, 1 H).

[1189]

(2)5-methoxy-3-methyl-1-benzofuran

A mixture of (2-acetyl-4-methoxyphenoxy)acetic acid (10.0 g) synthesized above, acetic anhydride (18.3 g) and acetic acid (100 mL) was stirred at 110°C for 5 hr, poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% ethyl acetate/hexane) to give the title object compound (5.87 g, 81%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.21 (d, J=1.1 Hz, 3 H), 3.86 (s, 3 H), 6.85 - 6.91 (m, 1 H), 6.95 (d, J=2.7 Hz, 1 H), 7.33 (d, J=8.8 Hz, 1 H), 7.35 - 7.39 (m, 1 H).

[1190]

(3)2-ethyl-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)butan-1-one

To a mixture of 5-methoxy-3-methyl-1-benzofuran (2.00 g) synthesized above, 2-ethylbutanoyl chloride (1.85 mL) and nitromethane (30 mL) was added aluminum chloride (3.28 g), and the mixture was stirred at room temperature for 1.5 hr. Water was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (6% ethyl acetate/hexane) to give the title object compound (3.12 g, 97%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 - 0.95 (m, 6 H), 1.52 - 1.66

(m, 2 H), 1.72 - 1.88 (m, 2 H), 2.59 (s, 3 H), 3.29 - 3.41 (m, 1 H), 3.88 (s, 3 H), 7.00 - 7.02 (m, 1 H), 7.06 - 7.11 (m, 1 H), 7.37 - 7.42 (m, 1 H).

[1191]

(4) methyl 4-{[2-ethyl-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)butyl]amino}benzoate

To a mixture of 2-ethyl-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)butan-1-one (800 mg) synthesized above, methyl 4-aminobenzoate (464 mg), triethylamine (3.43 mL) and methylene chloride (10 mL) was added titanium (IV) chloride (404 µL), and the mixture was stirred overnight at room temperature under argon atmosphere. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, methylene chloride was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (20 mL) of the obtained oil in tetrahydrofuran were added acetic acid (882 µL) and sodium cyanoborohydride (386 mg), and the mixture was stirred at room temperature for 1.5 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give the title object compound (718 mg, 59%) as a brown oil. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 (t, J=7.4 Hz, 3 H), 0.95 (t, J=7.3 Hz, 3 H), 1.14 - 1.74 (m, 4 H), 1.81 - 1.95 (m, 1 H), 2.23 (s, 3 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 4.47 - 4.53 (m, 1 H), 4.59 (t, J=8.1 Hz, 1 H), 6.56 (d, J=8.8 Hz, 2 H), 6.81 (dd, J=8.8, 2.6 Hz, 1 H), 6.86 (d, J=2.6 Hz, 1 H), 7.24 (d, J=8.8 Hz, 1 H), 7.79 (d, J=8.8 Hz, 2 H).

[1192]

(5)4-{[2-ethyl-1-(5-methoxy-3-methyl-1-benzofuran-2-

yl)butyl]amino}benzoic acid

To a mixture of methyl 4-{[2-ethyl-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)butyl]amino}benzoate (718 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (5.00 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (5.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (574 mg, 83%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 (t, J=7.4 Hz, 3 H), 0.95 (t, J=7.3 Hz, 3 H), 1.16 - 1.74 (m, 4 H), 1.82 - 1.95 (m, 1 H), 2.24 (s, 3 H), 3.83 (s, 3 H), 4.54 - 4.66 (m, 2 H), 6.58 (d, J=8.8 Hz, 2 H), 6.83 (dd, J=8.8, 2.6 Hz, 1 H), 6.88 (d, J=2.6 Hz, 1 H), 7.25 (d, J=8.8 Hz, 1 H), 7.85 (d, J=8.8 Hz, 2 H).

[1193]

(6) ethyl 3-{[(4-{[2-ethyl-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[2-ethyl-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)butyl]amino}benzoic acid (250 mg) synthesized above, β-alanine ethyl ester hydrochloride (151 mg), 1-hydroxybenzotriazole monohydrate (151 mg), triethylamine (275 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (188 mg), and the mixture was stirred at room temperature for 1 day. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (55% ethyl acetate/hexane) to give the title object compound (85.0 mg, 27%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.87 (t, J=7.4 Hz, 3 H), 0.95 (t,

511

J=7.4 Hz, 3 H), 1.24 (t, J=7.1 Hz, 3 H), 1.30 - 1.74 (m, 4 H), 1.81 - 1.93 (m, 1 H), 2.23 (s, 3 H), 2.54 - 2.62 (m, 2 H), 3.65 (q, J=6.1 Hz, 2 H), 3.83 (s, 3 H), 4.13 (q, J=7.1 Hz, 2 H), 4.40 (d, J=8.8 Hz, 1 H), 4.52 - 4.60 (m, 1 H), 6.53 - 6.62 (m, 3 H), 6.78 - 6.84 (m, 1 H), 6.86 (d, J=2.7 Hz, 1 H), 7.22 (s, 1 H), 7.54 (d, J=8.8 Hz, 2 H).

[1194]

(7)3-{[(4-{[2-ethyl-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[2-ethyl-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl]amino}propanoate (85.0 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (75.4 mg, 94%) as a white solid.

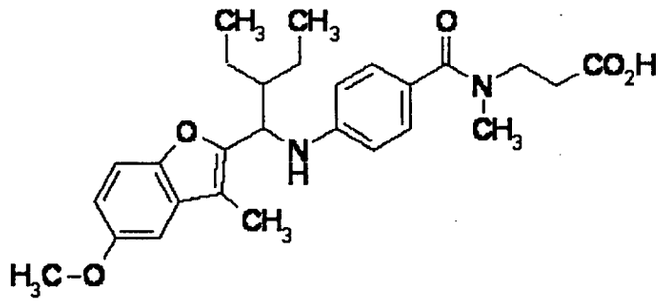
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 (t, J=7.3 Hz, 3 H), 0.94 (t, J=7.3 Hz, 3 H), 1.14 - 1.72 (m, 4 H), 1.79 - 1.93 (m, 1 H), 2.22 (s, 3 H), 2.62 (t, J=5.7 Hz, 2 H), 3.58 - 3.68 (m, 2 H), 3.82 (s, 3 H), 4.57 (d, J=7.7 Hz, 1 H), 6.52 - 6.62 (m, 3 H), 6.81 (dd, J=8.9, 2.5 Hz, 1 H), 6.86 (d, J=2.5 Hz, 1 H), 7.24 (d, J=8.9 Hz, 1 H), 7.52 (d, J=8.9 Hz, 2 H).

[1195]

Example A105

3-{[(4-{[2-ethyl-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1196]



[1197]

(1) ethyl 3-{[(4-{[2-ethyl-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[2-ethyl-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)butyl]amino}benzoic acid (250 mg) synthesized in Example A104(5), ethyl 3-(methylamino)propanoate (129 mg), 1-hydroxybenzotriazole monohydrate (151 mg), triethylamine (275 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (188 mg), and the mixture was stirred at room temperature for 1 day. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (55% ethyl acetate/hexane) to give the title object compound (261 mg, 81%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 (t, J=7.4 Hz, 3 H), 0.94 (t, J=7.4 Hz, 3 H), 1.23 (t, J=7.1 Hz, 3 H), 1.29 - 1.73 (m, 4 H), 1.79 - 1.93 (m, 1 H), 2.22 (s, 3 H), 2.61 (t, J=7.1 Hz, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.1 Hz, 2 H), 3.83 (s, 3 H), 4.11 (q, J=7.1 Hz, 2 H), 4.28 (d, J=8.5 Hz, 1 H), 4.50 - 4.58 (m, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.79 - 6.83 (m, 1 H), 6.86 (d, J=2.5 Hz, 1 H), 7.20 (d, J=8.7 Hz, 2 H), 7.24 (d, J=8.8 Hz, 1 H).

[1198]

(2)3-{[(4-{[2-ethyl-1-(5-methoxy-3-methyl-1-benzofuran-2-

yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[2-ethyl-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoate (261 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (231 mg, 94%) as a pale-brown solid.

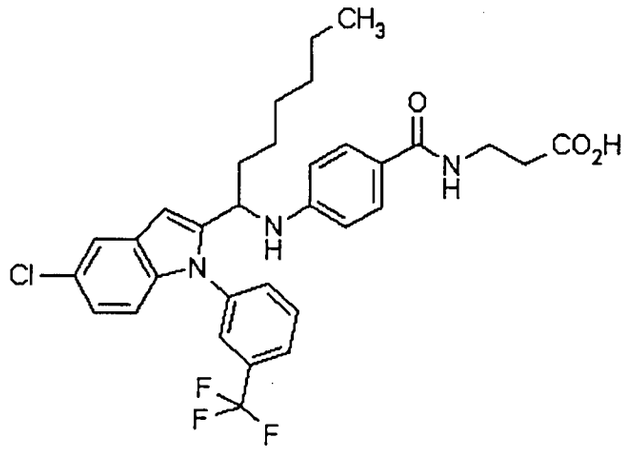
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 (t, J=7.3 Hz, 3 H), 0.94 (t, J=7.4 Hz, 3 H), 1.15 - 1.73 (m, 4 H), 1.80 - 1.93 (m, 1 H), 2.23 (s, 3 H), 2.65 (t, J=6.6 Hz, 2 H), 3.03 (s, 3 H), 3.69 (t, J=6.6 Hz, 2 H), 3.83 (s, 3 H), 4.55 (d, J=7.7 Hz, 1 H), 6.56 (d, J=8.9 Hz, 2 H), 6.82 (dd, J=8.8, 2.4 Hz, 1 H), 6.87 (d, J=2.4 Hz, 1 H), 7.20 - 7.28 (m, 3 H).

[1199]

Example A106

3-[({4-[(1-{5-chloro-1-[3-(trifluoromethyl)phenyl]-1H-indol-2-yl}heptyl)amino]phenyl}carbonyl)amino]propanoic acid

[1200]




[1201]

(1)5-chloro-N-methoxy-N-methyl-1H-indole-2-carboxamide

To a mixture of 5-chloro-1H-indole-2-carboxylic acid (15.0 g), N,O-dimethylhydroxylamine hydrochloride (8.97 g), 1-hydroxybenzotriazole monohydrate (14.1 g), triethylamine (25.6 mL) and N,N-dimethylformamide (200 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (17.6 g), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to quench the reaction, the resulting precipitate was collected by filtration to give the title object compound (15.5 g, 84%) as a pale-brown solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.43 (s, 3 H), 3.85 (s, 3 H), 7.14 - 7.18 (m, 1 H), 7.25 (dd, J=8.7, 1.9 Hz, 1 H), 7.36 (d, J=8.7 Hz, 1 H), 7.66 (d, J=1.9 Hz, 1 H), 9.32 (br s, 1 H).
[1202]
(2)1-(5-chloro-1H-indol-2-yl)heptan-1-one

To a solution (100 mL) of 5-chloro-N-methoxy-N-methyl-1H-indole-2-carboxamide (9.14 g) synthesized above in tetrahydrofuran was added a 2.3M solution (50.0 mL) of hexyllithium in hexane at -78°C, and the mixture was stirred under nitrogen atmosphere for 1.5 hr. A 2.3M solution (38.3 mL) of hexyllithium in hexane was additionally added, and the mixture was stirred at -78°C for 2 hr. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with hexane to give the title object compound (6.90 g, 68%) as a pale-yellow solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 - 0.95 (m, 3 H), 1.26 - 1.48 (m, 6 H), 1.71 - 1.85 (m, 2 H), 2.92 (t, J=7.7 Hz, 2 H), 7.11 - 7.14 (m, 1 H), 7.29 (dd, J=8.8, 1.9 Hz, 1 H), 7.36 (d, J=8.8 Hz, 1 H), 7.66 - 7.70 (m, 1 H), 9.05 - 9.19 (m, 1 H).
[1203]
(3)1-{5-chloro-1-[3-(trifluoromethyl)phenyl]-1H-indol-2-yl}heptan-1-one

A mixture of 1-(5-chloro-1H-indol-2-yl)heptan-1-one (9.14

g) synthesized above, 3-iodobenzotrifluoride (1.97 mL), copper (I) bromide (327 mg), potassium carbonate (2.36 g) and N-methyl-2-pyrrolidone (30 mL) was deaerated, and the mixture was stirred under argon atmosphere at 180°C for 1 day. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% ethyl acetate/hexane) to give the title object compound (0.78 g, 17%) as a brown oil. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 - 0.92 (m, 3 H), 1.22 - 1.41 (m, 6 H), 1.62 - 1.74 (m, 2 H), 2.90 - 2.97 (m, 2 H), 6.95 (d, J=8.8 Hz, 1 H), 7.25 (dd, J=8.8, 1.9 Hz, 1 H), 7.35 (s, 1 H), 7.42 - 7.47 (m, 1 H), 7.49 - 7.53 (m, 1 H), 7.59 - 7.66 (m, 1 H), 7.69 - 7.74 (m, 2 H).

[1204]

(4) methyl 4-[(1-{5-chloro-1-[3-(trifluoromethyl)phenyl]-1H-indol-2-yl}heptyl)amino]benzoate

To a mixture of 1-{5-chloro-1-[3-(trifluoromethyl)phenyl]-1H-indol-2-yl}heptan-1-one (709 mg) synthesized above, methyl 4-aminobenzoate (263 mg), triethylamine (1.94 mL) and methylene chloride (10 mL) was added titanium (IV) chloride (229 µL), and the mixture was stirred under argon atmosphere overnight at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (10 mL) of the obtained oil in tetrahydrofuran were added acetic acid (498 µL) and sodium cyanoborohydride (219 mg), and the mixture was stirred at room temperature for 1.5 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine,

dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15% ethyl acetate/hexane) to give the title object compound (645 mg, 68%) as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 (t, J=6.9 Hz, 3 H), 1.12 - 1.41 (m, 8 H), 1.74 - 1.93 (m, 2 H), 3.83 (s, 3 H), 4.03 - 4.15 (m, 1 H), 4.41 - 4.52 (m, 1 H), 6.33 (d, J=8.8 Hz, 2 H), 6.57 (s, 1 H), 6.88 (d, J=8.8 Hz, 1 H), 7.09 (dd, J=8.8, 1.9 Hz, 1 H), 7.45 - 7.52 (m, 1 H), 7.54 - 7.65 (m, 3 H), 7.68 - 7.79 (m, 3 H).

[1205]

(5)4-[(1-{5-chloro-1-[3-(trifluoromethyl)phenyl]-1H-indol-2-yl}heptyl)amino]benzoic acid

To a mixture of methyl 4-[(1-{5-chloro-1-[3-(trifluoromethyl)phenyl]-1H-indol-2-yl}heptyl)amino]benzoate (645 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (5.00 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (5.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (589 mg, 94%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.80 (t, J=6.8 Hz, 3 H), 1.03 - 1.34 (m, 6 H), 1.63 - 1.83 (m, 2 H), 4.29 - 4.44 (m, 1 H), 6.18 (d, J=8.3 Hz, 2 H), 6.49 (s, 1 H), 6.82 (d, J=8.5 Hz, 1 H), 7.02 (dd, J=8.5, 1.9 Hz, 1 H), 7.34 - 7.56 (m, 4 H), 7.60 (d, J=7.6 Hz, 1 H), 7.70 (d, J=8.3 Hz, 2 H).

[1206]

(6) ethyl 3-[({4-[(1-{5-chloro-1-[3-(trifluoromethyl)phenyl]-1H-indol-2-yl}heptyl)amino]phenyl}carbonyl)amino]propanoate

To a mixture of 4-[(1-{5-chloro-1-[3-(trifluoromethyl)phenyl]-1H-indol-2-yl}heptyl)amino]benzoic acid (250 mg) synthesized above, β-alanine ethyl ester hydrochloride (109 mg), 1-hydroxybenzotriazole monohydrate

(109 mg), triethylamine (198 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (136 mg), and the mixture was stirred at room temperature for 3 days. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% ethyl acetate/hexane) to give the title object compound (272 mg, 92%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.83 (t, J=6.7 Hz, 3 H), 1.11 - 1.39 (m, 11 H), 1.75 - 1.90 (m, 2 H), 2.60 (t, J=5.8 Hz, 2 H), 3.63 - 3.72 (m, 2 H), 3.93 - 4.04 (m, 1 H), 4.15 (q, J=7.1 Hz, 2 H), 4.38 - 4.50 (m, 1 H), 6.35 (d, J=8.5 Hz, 2 H), 6.53 - 6.64 (m, 2 H), 6.87 (d, J=8.6 Hz, 1 H), 7.08 (dd, J=8.6, 2.1 Hz, 1 H), 7.45 - 7.66 (m, 6 H), 7.70 (d, J=7.1 Hz, 1 H).

[1207]

(7)3-[({4-[(1-{5-chloro-1-[3-(trifluoromethyl)phenyl]-1H-indol-2-yl}heptyl)amino]phenyl}carbonyl)amino]propanoic acid

To a mixture of ethyl 3-[({4-[(1-{5-chloro-1-[3-(trifluoromethyl)phenyl]-1H-indol-2-yl}heptyl)amino]phenyl}carbonyl)amino]propanoate (273 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (5.00 mL), and the mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (5.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (253 mg, 97%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.78 (t, J=6.8 Hz, 3 H), 1.01 - 1.32 (m, 8 H), 1.64 - 1.78 (m, 2 H), 2.30 - 2.43 (m, 2 H), 3.37 - 3.53 (m, 2 H), 4.29 - 4.43 (m, 1 H), 6.27 (d, J=8.7 Hz, 2 H), 6.47 (s, 1 H), 6.76 - 6.89 (m, 2 H), 7.00 (dd, J=8.7,

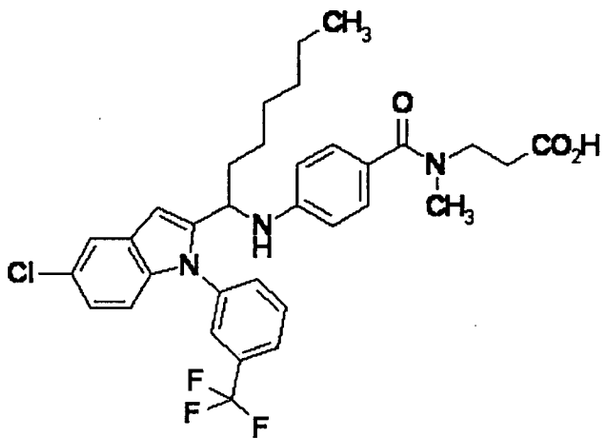
1.9 Hz, 1 H), 7.39 - 7.59 (m, 6 H), 7.63 (d, J=7.6 Hz, 1 H).

[1208]

Example A107

3-[({4-[(1-{5-chloro-1-[3-(trifluoromethyl)phenyl]-1H-indol-2-yl}heptyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[1209]



[1210]

(1) ethyl 3-[({4-[(1-{5-chloro-1-[3-(trifluoromethyl)phenyl]-1H-indol-2-yl}heptyl)amino]phenyl}carbonyl)(methyl)amino]propanoate

To a mixture of 4-[(1-{5-chloro-1-[3-(trifluoromethyl)phenyl]-1H-indol-2-yl}heptyl)amino]benzoic acid (250 mg) synthesized in Example A106(5), ethyl 3-(methylamino)propanoate (93.1 mg), 1-hydroxybenzotriazole monohydrate (109 mg), triethylamine (198 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (136 mg), and the mixture was stirred at room temperature for 3 days. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (40% ethyl acetate/hexane) to give the title object compound (254 mg,

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84%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.83 (t, J=6.9 Hz, 3 H), 1.11 - 1.37 (m, 11 H), 1.76 - 1.86 (m, 2 H), 2.62 (t, J=7.3 Hz, 2 H), 3.02 (s, 3 H), 3.72 (t, J=7.3 Hz, 2 H), 3.88 (d, J=7.7 Hz, 1 H), 4.07 - 4.17 (m, 2 H), 4.35 - 4.46 (m, 1 H), 6.34 (d, J=8.5 Hz, 2 H), 6.56 (s, 1 H), 6.88 (d, J=8.8 Hz, 1 H), 7.08 (dd, J=8.8, 2.0 Hz, 1 H), 7.17 (d, J=8.5 Hz, 2 H), 7.51 (d, J=7.7 Hz, 1 H), 7.56 (d, J=2.0 Hz, 1 H), 7.57 - 7.66 (m, 2 H), 7.71 (d, J=7.7 Hz, 1 H).

[1211]

(2)3-[({4-[(1-{5-chloro-1-[3-(trifluoromethyl)phenyl]-1H-indol-2-yl}heptyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

To a mixture of ethyl 3-[({4-[(1-{5-chloro-1-[3-(trifluoromethyl)phenyl]-1H-indol-2-yl}heptyl)amino]phenyl}carbonyl)(methyl)amino]propanoate (254 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred overnight at room temperature, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (223 mg, 92%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.81 (t, J=6.8 Hz, 3 H), 1.06 - 1.35 (m, 8 H), 1.70 - 1.82 (m, 2 H), 2.39 - 2.49 (m, 2 H), 2.92 (s, 3 H), 3.51 - 3.72 (m, 2 H), 4.38 (t, J=6.8 Hz, 1 H), 6.32 (d, J=8.5 Hz, 2 H), 6.53 (s, 1 H), 6.86 (d, J=8.7 Hz, 1 H), 7.05 (dd, J=8.7, 1.9 Hz, 1 H), 7.14 (d, J=8.5 Hz, 2 H), 7.47 - 7.55 (m, 2 H), 7.55 - 7.67 (m, 2 H), 7.70 (d, J=7.6 Hz, 1 H).

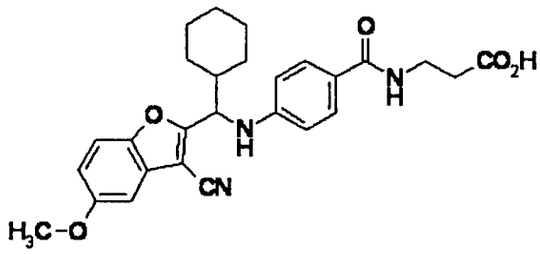
[1212]

Example A108

3-{[(4-{[(3-cyano-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic

acid

[1213]



[1214]

(1) (3-bromo-5-methoxy-1-benzofuran-2-yl) (cyclohexyl) methanone

To a mixture of dimethyl sulfoxide (831 mL) and tetrahydrofuran (20 mL) was added trifluoroacetic acid anhydride (1.63 mL) at -78°C, and the mixture was stirred for 30 min, and a solution (20 mL) of (3-bromo-5-methoxy-1-benzofuran-2-yl) (cyclohexyl) methanol (2.03 g) synthesized in Example A102(4) in tetrahydrofuran was added. The reaction mixture was stirred under argon atmosphere at -78°C for 1 hr, triethylamine (3.33 mL) was added, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (15% ethyl acetate/hexane) to give the title object compound (1.52 g, 75%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.20 - 1.63 (m, 5 H), 1.70 - 1.81 (m, 1 H), 1.82 - 2.00 (m, 4 H), 3.13 - 3.24 (m, 1 H), 3.95 (s, 3 H), 7.12 (d, J=9.3 Hz, 1 H), 7.46 - 7.50 (m, 2 H).

[1215]

(2) methyl 4-{[(3-bromo-5-methoxy-1-benzofuran-2-yl) (cyclohexyl) methyl] amino} benzoate

To a mixture of (3-bromo-5-methoxy-1-benzofuran-2-yl) (cyclohexyl) methanone (1.52 g) synthesized above, methyl 4-aminobenzoate (682 mg), triethylamine (5.03 mL) and methylene chloride (20 mL) was added titanium (IV) chloride (593 µL), and the mixture was stirred under argon atmosphere overnight

at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (20 mL) of the obtained oil in tetrahydrofuran were added acetic acid (1.29 mL) and sodium cyanoborohydride (567 mg), and the mixture was stirred at room temperature for 1.5 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, tetrahydrofuran was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% ethyl acetate/hexane) to give the title object compound (1.46 g, 69%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 - 1.38 (m, 5 H), 1.54 - 1.85 (m, 4 H), 1.85 - 2.01 (m, 2 H), 3.82 (s, 3 H), 3.90 (s, 3 H), 4.36 - 4.56 (m, 2 H), 6.54 (s, 1 H), 6.58 (d, J=9.0 Hz, 2 H), 6.86 (d, J=8.8 Hz, 1 H), 7.30 (d, J=8.8 Hz, 1 H), 7.81 (d, J=9.0 Hz, 2 H).

[1216]

(3)4-{[(3-cyano-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}benzoic acid

To a mixture of methyl 4-{[(3-bromo-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}benzoate (1.46 g) synthesized above, zinc cyanide (362 mg) and N,N-dimethylformamide (30 mL) was added tetrakis(triphenylphosphine)palladium (0) (357 mg), and after deaeration, the mixture was stirred under argon atmosphere at 80°C overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified

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by silica gel column chromatography (40% ethyl acetate/hexane) to give a yellow solid. To a solution (10 mL) of the obtained solid in tetrahydrofuran was added 1N lithium hydroxide aqueous solution (2.88 mL), and the mixture was stirred overnight with heating under reflux. Ethanol (10 mL) and water (10 mL) were added to the reaction mixture, and the mixture was stirred with heating under reflux for 3 hr. 1N lithium hydroxide aqueous solution (1.44 mL) was additionally added , and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (4.35 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (547 mg, 94%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.05 - 1.38 (m, 5 H), 1.53 - 1.87 (m, 4 H), 1.87 - 2.01 (m, 2 H), 3.94 (s, 3 H), 4.42 - 4.60 (m, 2 H), 6.58 (d, J=8.8 Hz, 2 H), 6.68 (d, J=0.8 Hz, 1 H), 6.84 (d, J=9.1 Hz, 1 H), 7.53 (dd, J=9.1, 0.8 Hz, 1 H), 7.87 (d, J=8.8 Hz, 2 H).

[1217]

(4) ethyl 3-{[(4-{[(3-cyano-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[(3-cyano-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}benzoic acid (240 mg) synthesized above, β-alanine ethyl ester hydrochloride (137 mg), 1-hydroxybenzotriazole monohydrate (136 mg), triethylamine (248 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (171 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60% ethyl

acetate/hexane) to give the title object compound (285 mg, 95%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.05 - 1.37 (m, 8 H), 1.53 - 1.86 (m, 4 H), 1.86 - 2.00 (m, 2 H), 2.59 (t, J=6.3 Hz, 2 H), 3.62 - 3.70 (m, 2 H), 3.93 (s, 3 H), 4.14 (q, J=7.1 Hz, 2 H), 4.35 - 4.45 (m, 2 H), 6.57 (d, J=8.8 Hz, 2 H), 6.60 (t, J=5.2 Hz, 1 H), 6.65 (d, J=0.5 Hz, 1 H), 6.83 (d, J=9.1 Hz, 1 H), 7.51 - 7.60 (m, 3 H).

[1218]

(5)3-{[(4-{[(3-cyano-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[(3-cyano-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoate (285 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (246 mg, 92%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 - 1.37 (m, 5 H), 1.50 - 1.63 (m, 1 H), 1.63 - 1.85 (m, 3 H), 1.85 - 2.01 (m, 2 H), 2.64 (t, J=5.7 Hz, 2 H), 3.60 - 3.70 (m, 2 H), 3.93 (s, 3 H), 4.42 (d, J=6.4 Hz, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 6.62 - 6.70 (m, 2 H), 6.83 (d, J=9.2 Hz, 1 H), 7.50 - 7.59 (m, 3 H).

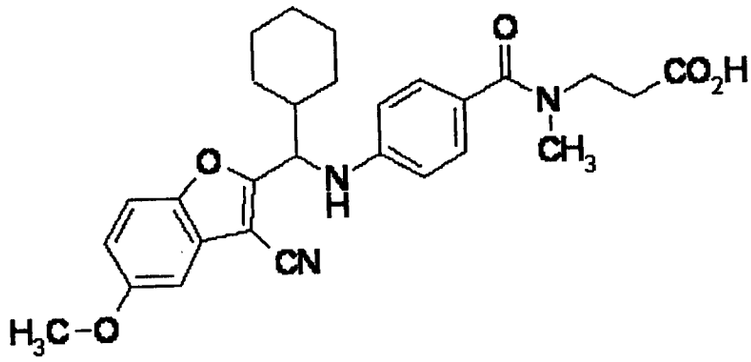
[1219]

Example A109

3-{[(4-{[(3-cyano-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[1220]

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[1221]

(1) ethyl 3-{[(4-{[(3-cyano-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate

To a mixture of 4-{[(3-cyano-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}benzoic acid (240 mg) synthesized in Example A108(3), ethyl 3-(methylamino)propanoate (117 mg), 1-hydroxybenzotriazole monohydrate (136 mg), triethylamine (248 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (171 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60% ethyl acetate/hexane) to give the title object compound (253 mg, 82%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 - 1.36 (m, 8 H), 1.52 - 1.85 (m, 4 H), 1.85 - 1.99 (m, 2 H), 2.62 (t, J=6.9 Hz, 2 H), 3.02 (s, 3 H), 3.71 (t, J=6.9 Hz, 2 H), 3.94 (s, 3 H), 4.11 (q, J=7.1 Hz, 2 H), 4.27 - 4.33 (m, 1 H), 4.35 - 4.43 (m, 1 H), 6.56 (d, J=8.5 Hz, 2 H), 6.66 - 6.67 (m, 1 H), 6.83 (d, J=9.1 Hz, 1 H), 7.23 (d, J=8.5 Hz, 2 H), 7.52 (dd, J=9.1, 0.8 Hz, 1 H).

[1222]

(2)3-{[(4-{[(3-cyano-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

To a mixture of ethyl 3-{[(4-{[(3-cyano-5-methoxy-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (253 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 3 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (218 mg, 91%) as a pale-yellow solid.

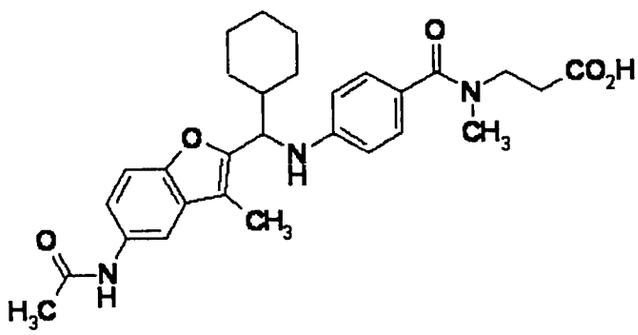
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 - 1.36 (m, 5 H), 1.53 - 1.63 (m, 1 H), 1.63 - 1.84 (m, 3 H), 1.85 - 2.00 (m, 2 H), 2.61 - 2.73 (m, 2 H), 3.05 (s, 3 H), 3.71 (t, J=6.6 Hz, 2 H), 3.94 (s, 3 H), 4.40 (d, J=6.4 Hz, 1 H), 6.57 (d, J=8.7 Hz, 2 H), 6.67 (d, J=0.8 Hz, 1 H), 6.84 (d, J=9.1 Hz, 1 H), 7.26 (d, J=8.7 Hz, 2 H), 7.55 (dd, J=9.1, 0.8 Hz, 1 H).

[1223]

Example A110

3-[{[4-({[5-(acetylamino)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoic acid

[1224]




[1225]

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(1)cyclohexyl(3-methyl-5-nitro-1-benzofuran-2-yl)methanone

To a mixture of 2'-hydroxy-5'-nitroacetophenone (5.00 g), 2-bromo-1-cyclohexylethanone (6.79 g) synthesized in Example A51(1) and N,N-dimethylformamide (50 mL) was added potassium carbonate (7.63 g), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title object compound (4.18 g, 53%) as a yellow solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.19 - 1.54 (m, 5 H), 1.70 - 1.81 (m, 1 H), 1.82 - 1.92 (m, 2 H), 1.92 - 2.02 (m, 2 H), 2.65 (s, 3 H), 3.24 - 3.36 (m, 1 H), 7.62 (d, J=9.2 Hz, 1 H), 8.37 (dd, J=9.2, 2.4 Hz, 1 H), 8.59 (d, J=2.4 Hz, 1 H).

[1226]

(2) methyl 4-{[cyclohexyl(3-methyl-5-nitro-1-benzofuran-2-yl)methyl]amino}benzoate

To a mixture of cyclohexyl(3-methyl-5-nitro-1-benzofuran-2-yl)methanone (3.00 g) synthesized above, methyl 4-aminobenzoate (1.57 g), triethylamine (11.6 mL) and methylene chloride (40 mL) was added titanium (IV) chloride (1.37 mL), and the mixture was stirred overnight under argon atmosphere at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (40 mL) of the obtained oil in tetrahydrofuran were added acetic acid (2.98 mL) and sodium cyanoborohydride (1.31 g), and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate,

and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% ethyl acetate/hexane) to give the title object compound (2.66 g, 61%) as an orange solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 1.38 (m, 5 H), 1.45 - 1.59 (m, 1 H), 1.62 - 2.01 (m, 4 H), 2.05 - 2.15 (m, 1 H), 2.32 (s, 3 H), 3.81 (s, 3 H), 4.41 - 4.56 (m, 2 H), 6.55 (d, J=9.1 Hz, 2 H), 7.43 (d, J=8.9 Hz, 1 H), 7.80 (d, J=9.1 Hz, 2 H), 8.16 (dd, J=8.9, 2.4 Hz, 1 H), 8.36 (d, J=2.4 Hz, 1 H).

[1227]

(3)4-{[cyclohexyl(3-methyl-5-nitro-1-benzofuran-2-yl)methyl]amino}benzoic acid

To a mixture of methyl 4-{[cyclohexyl(3-methyl-5-nitro-1-benzofuran-2-yl)methyl]amino}benzoate (2.66 g) synthesized above, tetrahydrofuran (20 mL) and ethanol (20 mL) was added 1N aqueous sodium hydroxide solution (20.0 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (40 mL), and 1N hydrochloric acid (20.0 mL) was added at 0°C. The resulting precipitate was collected by filtration and the obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title object compound (2.22 g, 86%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 1.40 (m, 5 H), 1.45 - 1.58 (m, 1 H), 1.63 - 2.02 (m, 4 H), 2.04 - 2.16 (m, 1 H), 2.33 (s, 3 H), 4.48 (d, J=8.0 Hz, 1 H), 6.57 (d, J=9.1 Hz, 2 H), 7.43 (d, J=8.9 Hz, 1 H), 7.86 (d, J=9.1 Hz, 2 H), 8.17 (dd, J=8.9, 2.4 Hz, 1 H), 8.37 (d, J=2.4 Hz, 1 H).

[1228]

(4) ethyl 3-{[(4-{[cyclohexyl(3-methyl-5-nitro-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[cyclohexyl(3-methyl-5-nitro-1-benzofuran-2-yl)methyl]amino}benzoic acid (1.54 g) synthesized

above, ethyl 3-(methylamino)propanoate (593 mg), 1-hydroxybenzotriazole monohydrate (692 mg), triethylamine (1.26 mL) and N,N-dimethylformamide (15 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (867 mg), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% ethyl acetate/hexane) to give the title object compound (1.41 g, 72%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 1.40 (m, 8 H), 1.44 - 1.56 (m, 1 H), 1.58 - 2.00 (m, 3 H), 2.06 - 2.17 (m, 1 H), 2.31 (s, 3 H), 2.61 (t, J=7.0 Hz, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.0 Hz, 2 H), 4.06 - 4.16 (m, 2 H), 4.28 - 4.34 (m, 1 H), 4.42 (t, J=8.0 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 7.22 (d, J=8.7 Hz, 2 H), 7.43 (d, J=9.1 Hz, 1 H), 8.16 (dd, J=9.1, 2.5 Hz, 1 H), 8.35 - 8.37 (m, 1 H).

[1229]

(5) ethyl 3-{[(4-{[(5-amino-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate

To a solution (20 mL) of ethyl 3-{[(4-{[cyclohexyl(3-methyl-5-nitro-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (600 mg) synthesized above in ethanol was added platinum (IV) oxide (60.0 mg), and the mixture was stirred under hydrogen atmosphere at room temperature for 1 hr. Platinum oxide was filtered off, and the filtrate was concentrated to give the title object compound (579 mg, quantitative) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.35 (m, 8 H), 1.49 - 1.60 (m, 1 H), 1.60 - 1.95 (m, 4 H), 2.01 - 2.12 (m, 1 H), 2.17 (s, 3 H), 2.61 (t, J=7.1 Hz, 2 H), 3.01 (s, 3 H), 3.56 (br s, 2 H),

3.70 (t, J=7.1 Hz, 2 H), 4.11 (q, J=7.1 Hz, 2 H), 4.30 - 4.34 (m, 2 H), 6.55 (d, J=8.7 Hz, 2 H), 6.59 (dd, J=8.5, 2.5 Hz, 1 H), 6.69 (d, J=2.5 Hz, 1 H), 7.14 (d, J=8.5 Hz, 1 H), 7.20 (d, J=8.7 Hz, 2 H).

[1230]

(6) ethyl 3-[{[4-({[5-(acetylamino)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoate

To a solution (10 mL) of ethyl 3-{[(4-{[(5-amino-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (480 mg) synthesized above in tetrahydrofuran were added triethylamine (204 µL) and acetic anhydride (138 µL), and the mixture was stirred at room temperature for 2.5 days. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (90% ethyl acetate/hexane) to give the title object compound (366 mg, 70%) as a pale-brown oil

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.38 (m, 8 H), 1.45 - 1.57 (m, 1 H), 1.60 - 1.97 (m, 4 H), 2.01 - 2.13 (m, 1 H), 2.17 (s, 3 H), 2.22 (s, 3 H), 2.61 (t, J=7.1 Hz, 2 H), 3.01 (s, 3 H), 3.71 (t, J=7.1 Hz, 2 H), 4.06 - 4.17 (m, 2 H), 4.31 - 4.41 (m, 2 H), 6.55 (d, J=8.5 Hz, 2 H), 7.09 (dd, J=8.8, 2.1 Hz, 1 H), 7.20 (d, J=8.5 Hz, 2 H), 7.26 (d, J=8.8 Hz, 1 H), 7.39 - 7.50 (m, 1 H), 7.71 (d, J=2.1 Hz, 1 H).

[1231]

(7)3-[{[4-({[5-(acetylamino)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoic acid

To a mixture of ethyl 3-[{[4-({[5-(acetylamino)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-

propanoate (366 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N lithium hydroxide aqueous solution (1.00 mL), and the mixture was stirred at room temperature for 1 hr. 1N Lithium hydroxide aqueous solution (1.00 mL) was additionally added, and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (292 mg, 84%) as a white solid.

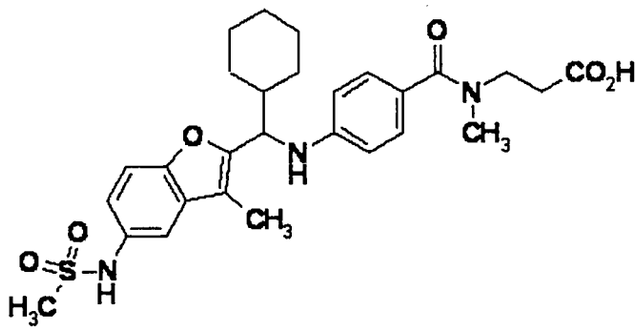
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.37 (m, 5 H), 1.45 - 1.57 (m, 1 H), 1.60 - 1.99 (m, 4 H), 2.04 - 2.25 (m, 7 H), 2.44 - 2.68 (m, 2 H), 2.99 (s, 3 H), 3.45 - 3.73 (m, 2 H), 4.35 (d, J=7.9 Hz, 1 H), 6.54 (d, J=8.7 Hz, 2 H), 7.03 - 7.11 (m, 1 H), 7.12 - 7.28 (m, 3 H), 7.57 - 7.68 (m, 2 H).

[1232]

Example A111

3-[({4-[(cyclohexyl{3-methyl-5-[(methylsulfonyl)amino]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[1233]



[1234]

To a solution (10 mL) of ethyl 3-{[(4-{[(5-amino-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (412 mg) synthesized in Example A110(5) in N,N-dimethylacetamide were added triethylamine (160 μL) and

methanesulfonyl chloride (89.0 μL), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60% ethyl acetate/hexane) to give a yellow oil. To a mixture of the obtained oil, tetrahydrofuran (5 mL), ethanol (5 mL) and water (1 mL) was added 4N lithium hydroxide aqueous solution (500 μL), and the mixture was stirred at room temperature for 4 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (379 mg, 91%) as a white solid.

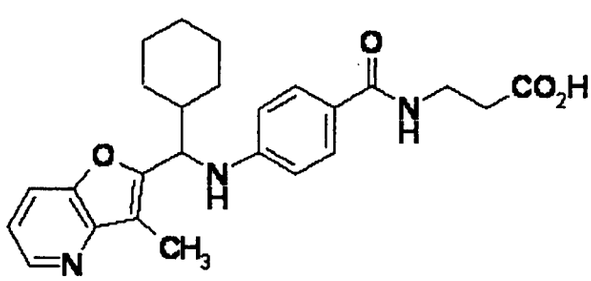
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.39 (m, 5 H), 1.45 - 1.57 (m, 1 H), 1.62 - 1.98 (m, 4 H), 2.06 - 2.15 (m, 1 H), 2.22 (s, 3 H), 2.64 (t, J=6.2 Hz, 2 H), 2.93 (s, 3 H), 3.03 (s, 3 H), 3.68 (t, J=6.2 Hz, 2 H), 4.37 (d, J=8.0 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.65 - 6.71 (m, 1 H), 7.06 (dd, J=8.6, 2.2 Hz, 1 H), 7.23 (d, J=8.7 Hz, 2 H), 7.31 (d, J=8.6 Hz, 1 H), 7.34 (d, J=2.2 Hz, 1 H).

[1235]

Example A112

3-{[(4-{[cyclohexyl(3-methylfuro[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1236]



[1237]

(1)cyclohexyl(3-methylfuro[3,2-b]pyridin-2-yl)methanone

To a mixture of 1-(3-hydroxypyridin-2-yl)ethanone (4.37 g), 2-bromo-1-cyclohexylethanone (9.82 g) synthesized in Example A51(1) and N,N-dimethylformamide (50 mL) was added potassium carbonate (13.2 g), and the mixture was stirred at room temperature for 2.5 days. 1N Hydrochloric acid was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over ~~magnesium sulfate~~, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give the title object compound (4.09 g, 53%) as a brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.19 - 1.59 (m, 5 H), 1.70 - 1.92 (m, 3 H), 1.92 - 2.03 (m, 2 H), 2.69 (s, 3 H), 3.26 - 3.39 (m, 1 H), 7.39 (dd, J=8.3, 4.6 Hz, 1 H), 7.82 (dd, J=8.3, 1.4 Hz, 1 H), 8.65 (dd, J=4.6, 1.4 Hz, 1 H).

[1238]

(2) methyl 4-{[cyclohexyl(3-methylfuro[3,2-b]pyridin-2-yl)methyl]amino}benzoate

To a mixture of cyclohexyl(3-methylfuro[3,2-b]pyridin-2-yl)methanone (1.08 g) synthesized above, methyl 4-aminobenzoate (738 mg), triethylamine (4.95 mL) and methylene chloride (20 mL) was added titanium (IV) chloride (584 μL), and the mixture was stirred under argon atmosphere overnight at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (20 mL) of the obtained oil in tetrahydrofuran were added acetic acid (1.27 mL) and sodium cyanoborohydride (558 mg), and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction,

tetrahydrofuran was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% ethyl acetate/hexane) to give the title object compound (789 mg, 47%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.99 - 1.38 (m, 5 H), 1.42 - 1.53 (m, 1 H), 1.64 - 2.01 (m, 4 H), 2.06 - 2.16 (m, 1 H), 2.77 (s, 3 H), 3.81 (s, 3 H), 4.50 - 4.63 (m, 2 H), 6.54 (d, J=9.1 Hz, 2 H), 7.37 (dd, J=8.2, 5.8 Hz, 1 H), 7.81 (d, J=9.1 Hz, 2 H), 7.98 (dd, J=8.2, 1.1 Hz, 1 H), 8.49 (dd, J=5.8, 1.1 Hz, 1 H).

[1239]

(3)4-{[cyclohexyl(3-methylfuro[3,2-b]pyridin-2-yl)methyl]amino}benzoic acid

To a mixture of methyl 4-{[cyclohexyl(3-methylfuro[3,2-b]pyridin-2-yl)methyl]amino}benzoate (789 mg) synthesized above, tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N aqueous sodium hydroxide solution (10.0 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (10.0 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (718 mg, 94%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 1.39 (m, 5 H), 1.47 - 1.60 (m, 1 H), 1.62 - 2.02 (m, 4 H), 2.03 - 2.17 (m, 1 H), 2.38 (s, 3 H), 4.47 - 4.72 (m, 2 H), 6.58 (d, J=8.9 Hz, 2 H), 7.18 (dd, J=8.3, 4.9 Hz, 1 H), 7.65 (dd, J=8.3, 1.2 Hz, 1 H), 7.86 (d, J=8.9 Hz, 2 H), 8.51 (dd, J=4.9, 1.2 Hz, 1 H).

[1240]

(4) ethyl 3-{[(4-{[cyclohexyl(3-methylfuro[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[cyclohexyl(3-methylfuro[3,2-b]pyridin-2-yl)methyl]amino}benzoic acid (330 mg) synthesized

above, β-alanine ethyl ester hydrochloride (209 mg), 1-hydroxybenzotriazole monohydrate (208 mg), triethylamine (379 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (261 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (70% ethyl acetate/hexane) to give the title object compound (383 mg, 91%) as a pale-brown oil

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 1.38 (m, 8 H), 1.47 - 1.58 (m, 1 H), 1.61 - 2.00 (m, 4 H), 2.05 - 2.16 (m, 1 H), 2.35 (s, 3 H), 2.58 (t, J=5.8 Hz, 2 H), 3.61 - 3.69 (m, 2 H), 4.13 (q, J=7.1 Hz, 2 H), 4.42 - 4.52 (m, 2 H), 6.53 - 6.65 (m, 3 H), 7.13 (dd, J=8.2, 4.7 Hz, 1 H), 7.54 (d, J=8.8 Hz, 2 H), 7.58 - 7.62 (m, 1 H), 8.45 - 8.49 (m, 1 H).

[1241]

(5)3-{[(4-{[cyclohexyl(3-methylfuro[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclohexyl(3-methylfuro[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate (383 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred overnight at room temperature, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (315 mg, 88%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 - 1.38 (m, 5 H), 1.44 - 1.57 (m, 1 H), 1.61 - 2.00 (m, 4 H), 2.05 - 2.18 (m, 1 H), 2.35 (s, 3 H), 2.64 (t, J=5.7 Hz, 2 H), 3.56 - 3.78 (m, 2 H), 4.46 (d,

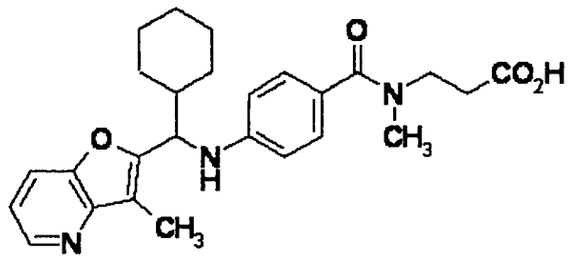
J=8.0 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.72 (t, J=6.1 Hz, 1 H), 7.18 (dd, J=8.3, 4.9 Hz, 1 H), 7.54 (d, J=8.7 Hz, 2 H), 7.66 (dd, J=8.3, 1.3 Hz, 1 H), 8.49 (dd, J=4.9, 1.3 Hz, 1 H).

[1242]

Example A113

3-{[(4-{[cyclohexyl(3-methylfuro[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1243]



[1244]

(1) ethyl 3-{[(4-{[cyclohexyl(3-methylfuro[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[cyclohexyl(3-methylfuro[3,2-b]pyridin-2-yl)methyl]amino}benzoic acid (330 mg) synthesized in Example A112(3), ethyl 3-(methylamino)propanoate (178 mg), 1-hydroxybenzotriazole monohydrate (208 mg), triethylamine (379 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (261 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (80% ethyl acetate/hexane) to give the title object compound (292 mg, 67%) as a pale-brown oil

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 - 1.38 (m, 8 H), 1.47 - 1.58 (m, 1 H), 1.61 - 2.00 (m, 4 H), 2.05 - 2.16 (m, 1 H), 2.35 (s, 3 H), 2.60 (t, J=6.9 Hz, 2 H), 3.00 (s, 3 H), 3.69 (t, J=6.9

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Hz, 2 H), 4.10 (q, J=7.0 Hz, 2 H), 4.35 (d, J=8.3 Hz, 1 H), 4.45 (t, J=8.3 Hz, 1 H), 6.56 (d, J=8.5 Hz, 2 H), 7.13 (dd, J=8.2, 4.9 Hz, 1 H), 7.20 (d, J=8.5 Hz, 2 H), 7.60 (dd, J=8.2, 1.4 Hz, 1 H), 8.47 (dd, J=4.9, 1.4 Hz, 1 H).

[1245]

(2)3-{[(4-{[cyclohexyl(3-methylfuro[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclohexyl(3-methylfuro[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (292 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and the mixture was acidified with acetic acid, and extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (278 mg, quantitative) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.39 (m, 5 H), 1.47 - 1.58 (m, 1 H), 1.61 - 2.00 (m, 4 H), 2.06 - 2.16 (m, 1 H), 2.34 (s, 3 H), 2.60 - 2.73 (m, 2 H), 3.03 (s, 3 H), 3.70 (t, J=6.8 Hz, 2 H), 4.45 (d, J=8.0 Hz, 1 H), 6.56 (d, J=8.5 Hz, 2 H), 7.17 (dd, J=8.2, 4.8 Hz, 1 H), 7.23 (d, J=8.5 Hz, 2 H), 7.65 (dd, J=8.2, 1.3 Hz, 1 H), 8.50 (dd, J=4.8, 1.3 Hz, 1 H).

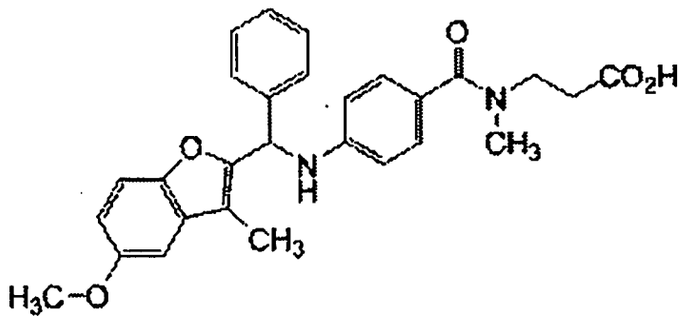
[1246]

Example A114

3-{[(4-{[(5-methoxy-3-methyl-1-benzofuran-2-yl)(phenyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[1247]

537



[1248]

(1) (5-methoxy-3-methyl-1-benzofuran-2-yl) (phenyl)methanone

To a mixture of 5-methoxy-3-methyl-1-benzofuran (2.00 g) synthesized in Example A104(2), benzoyl chloride (1.68 mL) and nitromethane (20 mL) was added aluminum chloride (3.28 g), and the mixture was stirred at room temperature for 2 hr. Water was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30% ethyl acetate/hexane) and further by silica gel column chromatography (20% ethyl acetate/hexane) to give the title object compound (2.03 g, 62%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.62 (s, 3 H), 3.89 (s, 3 H), 7.05 (d, J=2.5 Hz, 1 H), 7.10 (dd, J=9.1, 2.5 Hz, 1 H), 7.42 (d, J=9.1 Hz, 1 H), 7.47 - 7.63 (m, 3 H), 8.04 - 8.09 (m, 2 H).

[1249]

(2) methyl 4-{[(5-methoxy-3-methyl-1-benzofuran-2-yl) (phenyl)methyl]amino}benzoate

To a mixture of (5-methoxy-3-methyl-1-benzofuran-2-yl) (phenyl)methanone (2.03 g) synthesized above, methyl 4-aminobenzoate (1.27 g), triethylamine (8.50 mL) and methylene chloride (30 mL) was added titanium (IV) chloride (1.00 mL), and the mixture was stirred under argon atmosphere overnight at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, methylene chloride was evaporated in an evaporator, and the residue was

extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (30 mL) of the obtained oil in tetrahydrofuran were added acetic acid (2.18 mL) and sodium cyanoborohydride (955 mg), and the mixture was stirred at room temperature for 2.5 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, the organic solvent was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30% ethyl acetate/hexane) to give the title object compound (2.36 g, 77%) as a brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.26 (s, 3 H), 3.82 (s, 3 H), 3.84 (s, 3 H), 4.98 (d, J=6.0 Hz, 1 H), 5.82 (d, J=6.0 Hz, 1 H), 6.60 (d, J=8.7 Hz, 2 H), 6.84 (dd, J=8.8, 2.6 Hz, 1 H), 6.90 (d, J=2.6 Hz, 1 H), 7.23 - 7.37 (m, 4 H), 7.39 - 7.44 (m, 2 H), 7.82 (d, J=8.7 Hz, 2 H).

[1250]

(3)4-{[(5-methoxy-3-methyl-1-benzofuran-2-yl)(phenyl)methyl]amino}benzoic acid

To a mixture of methyl 4-{[(5-methoxy-3-methyl-1-benzofuran-2-yl)(phenyl)methyl]amino}benzoate (2.36 g) synthesized above, tetrahydrofuran (20 mL) and ethanol (20 mL) was added 1N aqueous sodium hydroxide solution (20.0 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (40 mL), and 1N hydrochloric acid (20.0 mL) was added at 0°C. The resulting precipitate was collected by filtration and the obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (1.09 g, 48%) as a pale-red solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.27 (s, 3 H), 3.84 (s, 3 H), 5.00 - 5.11 (m, 1 H), 5.84 (br s, 1 H), 6.61 (d, J=8.8 Hz, 2 H), 6.81 - 6.88 (m, 1 H), 6.91 (d, J=2.7 Hz, 1 H), 7.24 - 7.38 (m, 4 H), 7.39 - 7.45 (m, 2 H), 7.88 (d, J=8.8 Hz, 2 H).

[1251]

(4) ethyl 3-{[(4-{[(5-methoxy-3-methyl-1-benzofuran-2-yl)(phenyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate

To a mixture of 4-{[(5-methoxy-3-methyl-1-benzofuran-2-yl)(phenyl)methyl]amino}benzoic acid (400 mg) synthesized above, ethyl 3-(methylamino)propanoate (203 mg), 1-hydroxybenzotriazole monohydrate (237 mg), triethylamine (431 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (297 mg), and the mixture was stirred overnight at room temperature. Water was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (486 mg, 94%) as a pale-brown oil

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.24 (t, J=7.1 Hz, 3 H), 2.26 (s, 3 H), 2.56 - 2.67 (m, 2 H), 3.02 (s, 3 H), 3.71 (t, J=7.1 Hz, 2 H), 3.84 (s, 3 H), 4.12 (q, J=7.1 Hz, 2 H), 4.76 (d, J=6.0 Hz, 1 H), 5.77 (d, J=6.0 Hz, 1 H), 6.60 (d, J=8.5 Hz, 2 H), 6.84 (dd, J=8.9, 2.6 Hz, 1 H), 6.90 (d, J=2.6 Hz, 1 H), 7.20 - 7.37 (m, 6 H), 7.39 - 7.45 (m, 2 H).

[1252]

(5)3-{[(4-{[(5-methoxy-3-methyl-1-benzofuran-2-yl)(phenyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

To a mixture of ethyl 3-{[(4-{[(5-methoxy-3-methyl-1-benzofuran-2-

yl)(phenyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (486 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 3 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (412 mg, 90%) as a white solid.

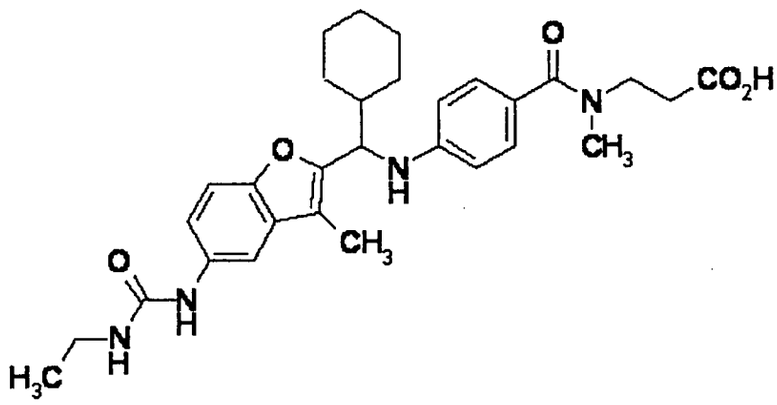
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.26 (s, 3 H), 2.68 (t, J=6.4 Hz, 2 H), 3.05 (s, 3 H), 3.72 (t, J=6.4 Hz, 2 H), 3.84 (s, 3 H), 5.78 (s, 1 H), 6.60 (d, J=8.7 Hz, 2 H), 6.84 (dd, J=8.9, 2.5 Hz, 1 H), 6.91 (d, J=2.5 Hz, 1 H), 7.23 - 7.39 (m, 6 H), 7.39 - 7.47 (m, 2 H).

[1253]

Example A115

3-[({4-[(cyclohexyl{5-[(ethylcarbamoyl)amino]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[1254]



[1255]

(1) ethyl 3-[({4-[(cyclohexyl{5-[(ethylcarbamoyl)amino]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate

To a solution (10 mL) of ethyl 3-{[(4-{[(5-amino-3-

methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (280 mg) synthesized in Example A110(5) in tetrahydrofuran were added triethylamine (95 μL) and ethyl isocyanate (54 μL), and the mixture was stirred at room temperature for 1 day. Triethylamine (95 μL) and ethyl isocyanate (54 μL) were additionally added, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (60 - 100% ethyl acetate/hexane) to give the title object compound (304 mg, 95%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.37 (m, 11 H), 1.44 - 1.57 (m, 1 H), 1.59 - 1.96 (m, 4 H), 2.04 - 2.15 (m, 1 H), 2.19 (s, 3 H), 2.56 - 2.66 (m, 2 H), 3.02 (s, 3 H), 3.14 - 3.28 (m, 2 H), 3.71 (t, J=7.0 Hz, 2 H), 4.11 (q, J=7.1 Hz, 2 H), 4.29 - 4.45 (m, 2 H), 6.55 (d, J=8.8 Hz, 2 H), 6.72 - 6.83 (m, 1 H), 7.15 - 7.23 (m, 3 H), 7.43 - 7.48 (m, 1 H).

[1256]

(2)3-[({4-[(cyclohexyl{5-[(ethylcarbamoyl)amino]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

To a mixture of ethyl 3-[({4-[(cyclohexyl{5-[(ethylcarbamoyl)amino]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate (304 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N lithium hydroxide aqueous solution (2.00 mL), and the mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (258 mg, 89%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.39 (m, 8 H), 1.45 - 1.57 (m, 1 H), 1.61 - 1.98 (m, 4 H), 2.06 - 2.20 (m, 4 H), 2.47 -

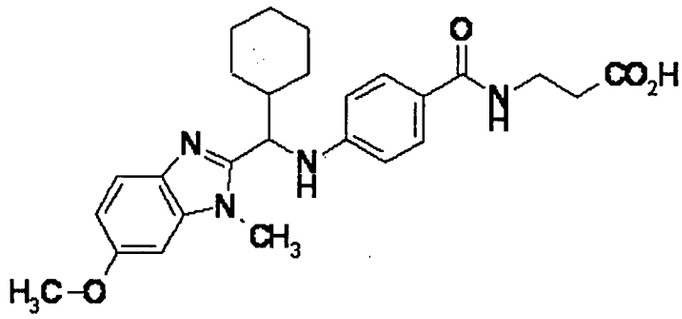
2.65 (m, 2 H), 2.99 (s, 3 H), 3.12 - 3.25 (m, 2 H), 3.52 - 3.70 (m, 2 H), 4.34 (d, J=8.1 Hz, 1 H), 4.94 - 5.06 (m, 1 H), 6.53 (d, J=8.7 Hz, 2 H), 6.88 (dd, J=8.7, 2.0 Hz, 1 H), 7.14 - 7.24 (m, 3 H), 7.35 (d, J=2.0 Hz, 1 H).

[1257]

Example A116

3-{[(4-{[cyclohexyl(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1258]



[1259]

(1)5-methoxy-N-methyl-2-nitroaniline

A mixture of formic acid (7.64 g) and acetic anhydride (16.9 g) was stirred at 60°C for 2 hr then a solution (100 mL) of 5-methoxy-2-nitroaniline (9.30 g) in tetrahydrofuran was added dropwise, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. To a solution (200 mL) of the residue in tetrahydrofuran was added a 1.0M solution (140 mL) of borane-tetrahydrofuran complex in tetrahydrofuran at 0°C, and the mixture was stirred with heating under reflux for 2 hr. Methanol was added to the reaction mixture at 0°C, and the mixture was stirred at room temperature for 30 min. After stirring, 1N hydrochloric acid was added to adjust to pH=2. The reaction mixture was stirred

with heating under reflux for 1 hr, and concentrated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed with water and saturated brine, dried over sodium sulfate, and concentrated under reduced pressure to give the title object compound (6.30 g, 62%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.01 (d, J = 5.1 Hz, 3H), 3.88 (s, 3H), 6.12 (d, J = 2.7 Hz, 1H), 6.24 (dd, J = 9.6, 2.4 Hz, 1H), 8.14 (d, J = 9.6 Hz, 1H), 8.29 (br, 1H).

[1260]

(2) 6-methoxy-1-methyl-1H-benzoimidazole

To a solution (200 mL) of 5-methoxy-N-methyl-2-nitroaniline (6.30 g) synthesized above in methanol was added 10% palladium/carbon (1.00 g) and the mixture was stirred under hydrogen atmosphere overnight at room temperature. Palladium/carbon was filtered off, and the filtrate was concentrated. A solution (150 mL) of the residue in formic acid was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% ethyl acetate/petroleum ether) to give the title object compound (4.07 g, 60%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.78 (s, 3H), 3.87 (s, 3H), 6.81 (d, J = 2.4 Hz, 1H), 6.91 (dd, J = 8.7, 2.4 Hz, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.75 (s, 1H).

[1261]

(3) N-methoxy-N-methylcyclohexanecarboxamide

A mixture of cyclohexanecarboxylic acid (6.10 g), N,O-dimethylhydroxyamine hydrochloride (7.31 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (14.4 g), N,N-diisopropylethylamine (9.68 g), 4-dimethylaminopyridine (600 mg) and methylene chloride (150 mL) was stirred overnight at room temperature. water was added to quench the reaction, and the reaction mixture was extracted with methylene chloride. The extract was washed with saturated brine, dried over sodium

sulfate, and concentrated under reduced pressure to give the title object compound (7.57 g, 88%).

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.21-1.30 (m, 3H), 1.42-1.50 (m, 2H), 1.64-1.80 (m, 5H), 2.65 (m, 1H), 3.14 (s, 3H), 3.66 (s, 3H).

[1262]

(4)cyclohexyl(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methanone

To a solution (100 mL) of 6-methoxy-1-methyl-1H-benzoimidazole (4.07 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added a 1.6M solution (30.1 mL) of n-butyllithium in hexane at -78°C, and the mixture was stirred under nitrogen atmosphere for 30 min. A solution (50 mL) of N-methoxy-N-methylcyclohexanecarboxamide (5.15 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added, and the mixture was stirred at -78°C for 1 hr and at room temperature for 2 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether=1:5, volume ratio) to give the title object compound (5.80 g, 85%) as white crystals.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.23-1.33 (m, 1H), 1.45-1.52 (m, 4H), 1.64-1.72 (m, 1H), 1.78-1.86 (m, 2H), 1.96-2.01 (m, 2H), 3.82-3.90 (m, 1H), 3.91 (s, 3H), 4.09 (s, 3H), 6.77 (d, J = 2.4 Hz, 1H), 7.00 (dd, J = 9.0, 2.4 Hz, 1H), 7.76 (dd, J = 9.0, 2.4 Hz, 1H).

[1263]

(5) methyl 4-{[cyclohexyl(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]amino}benzoate

To a mixture of cyclohexyl(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methanone (1.00 g) synthesized above, methyl 4-aminobenzoate (611 mg), triethylamine (4.10 mL) and

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methylene chloride (20 mL) was added titanium (IV) chloride (482 μL), and the mixture was stirred under argon atmosphere overnight at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, methylene chloride was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown solid. To a solution (20 mL) of the obtained solid in tetrahydrofuran were added acetic acid (1.05 mL) and sodium cyanoborohydride (461 mg), and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, tetrahydrofuran was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (625 mg, 42%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.34 (m, 5 H), 1.46 - 1.58 (m, 1 H), 1.59 - 1.84 (m, 4 H), 1.95 - 2.11 (m, 1 H), 3.77 (s, 3 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 4.59 (t, J=8.0 Hz, 1 H), 5.04 (d, J=8.0 Hz, 1 H), 6.63 (d, J=8.8 Hz, 2 H), 6.76 (d, J=2.4 Hz, 1 H), 6.88 (dd, J=8.7, 2.4 Hz, 1 H), 7.59 (d, J=8.7 Hz, 1 H), 7.80 (d, J=8.8 Hz, 2 H).

[1264]

(6)4-{[cyclohexyl(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]amino}benzoic acid

To a mixture of methyl 4-{[cyclohexyl(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]amino}benzoate (625 mg) synthesized above, tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N aqueous sodium hydroxide solution (5.00 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (5.00 mL)

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was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (600 mg, quantitative) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.01 - 1.36 (m, 5 H), 1.40 - 1.53 (m, 1 H), 1.56 - 1.86 (m, 3 H), 1.98 - 2.19 (m, 2 H), 3.83 (s, 3 H), 3.87 (s, 3 H), 4.59 - 4.69 (m, 1 H), 5.82 - 5.96 (m, 1 H), 6.68 (d, J=8.9 Hz, 2 H), 6.78 (d, J=2.3 Hz, 1 H), 6.91 (dd, J=8.9, 2.3 Hz, 1 H), 7.64 (d, J=8.9 Hz, 1 H), 7.88 (d, J=8.9 Hz, 2 H).

[1265]

(7) ethyl 3-{[(4-{[cyclohexyl(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[cyclohexyl(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]amino}benzoic acid (270 mg) synthesized above, β-alanine ethyl ester hydrochloride (158 mg), 1-hydroxybenzotriazole monohydrate (158 mg), triethylamine (287 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (198 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with 1N hydrochloric acid, saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60 - 100% ethyl acetate/hexane) to give the title object compound (151 mg, 45%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 - 1.35 (m, 8 H), 1.45 - 1.55 (m, 1 H), 1.58 - 1.85 (m, 3 H), 1.94 - 2.11 (m, 2 H), 2.58 (t, J=6.1 Hz, 2 H), 3.66 (q, J=6.1 Hz, 2 H), 3.76 (s, 3 H), 3.86 (s, 3 H), 4.14 (q, J=7.1 Hz, 2 H), 4.56 (t, J=7.8 Hz, 1 H), 4.90 (d, J=7.8 Hz, 1 H), 6.58 - 6.67 (m, 3 H), 6.75 (d, J=2.5 Hz, 1 H), 6.88 (dd, J=8.8, 2.5 Hz, 1 H), 7.55 (d, J=8.8 Hz, 2

H), 7.58 (d, J=8.8 Hz, 1 H).

[1266]

(8)3-{[(4-{[cyclohexyl(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclohexyl(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate (151 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 2.5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (124 mg, 87%) as a white solid.

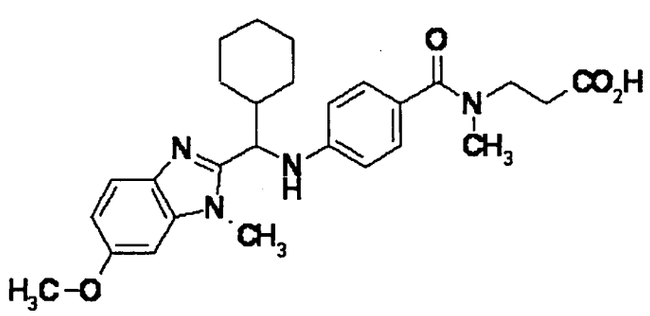
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 1.30 (m, 5 H), 1.30 - 1.40 (m, 1 H), 1.60 - 1.70 (m, 2 H), 1.71 - 1.83 (m, 1 H), 1.90 - 2.05 (m, 1 H), 2.12 - 2.23 (m, 1 H), 2.71 (t, J=5.4 Hz, 2 H), 3.72 - 3.84 (m, 2 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.57 - 4.66 (m, 1 H), 6.74 (d, J=8.9 Hz, 2 H), 6.78 (d, J=2.4 Hz, 1 H), 6.90 (dd, J=8.9, 2.4 Hz, 1 H), 7.24 - 7.32 (m, 1 H), 7.52 (d, J=8.9 Hz, 1 H), 7.66 (d, J=8.9 Hz, 2 H).

[1267]

Example A117

3-{[(4-{[cyclohexyl(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1268]



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[1269]

(1) ethyl 3-{[(4-{[cyclohexyl(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[cyclohexyl(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]amino}benzoic acid (270 mg) synthesized in Example A116(6), ethyl 3-(methylamino)propanoate (135 mg), 1-hydroxybenzotriazole monohydrate (158 mg), triethylamine (287 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (198 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with 1N hydrochloric acid, saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60 - 100% ethyl acetate/hexane) to give the title object compound (103 mg, 30%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.33 (m, 8 H), 1.45 - 1.55 (m, 1 H), 1.59 - 1.92 (m, 3 H), 1.92 - 2.13 (m, 2 H), 2.61 (t, J=7.0 Hz, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.0 Hz, 2 H), 3.76 (s, 3 H), 3.86 (s, 3 H), 4.11 (q, J=7.1 Hz, 2 H), 4.49 - 4.57 (m, 1 H), 4.75 (d, J=8.2 Hz, 1 H), 6.63 (d, J=8.5 Hz, 2 H), 6.76 (d, J=2.4 Hz, 1 H), 6.88 (dd, J=8.8, 2.4 Hz, 1 H), 7.22 (d, J=8.5 Hz, 2 H), 7.59 (d, J=8.8 Hz, 1 H).

[1270]

(2)3-{[(4-{[cyclohexyl(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclohexyl(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (103 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5

mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (72.1 mg, 74%) as a pale-brown solid.

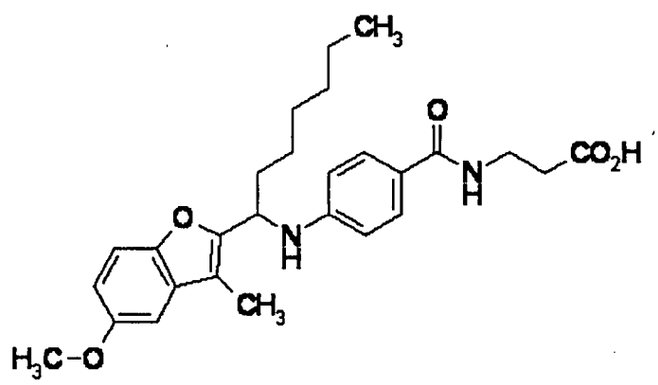
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 1.30 (m, 5 H), 1.31 - 1.41 (m, 1 H), 1.57 - 1.81 (m, 3 H), 1.88 - 2.03 (m, 1 H), 2.07 - 2.19 (m, 1 H), 2.69 - 2.81 (m, 2 H), 3.10 (s, 3 H), 3.73 - 3.82 (m, 2 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 4.54 (d, J=8.1 Hz, 1 H), 6.59 (d, J=8.5 Hz, 2 H), 6.77 (d, J=2.4 Hz, 1 H), 6.88 (dd, J=8.9, 2.4 Hz, 1 H), 7.20 - 7.28 (m, 2 H), 7.54 (d, J=8.9 Hz, 1 H).

[1271]

Example A118

3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)heptyl]amino}phenyl)carbonyl]amino}propanoic acid

[1272]



[1273]

(1)1-(5-methoxy-3-methyl-1-benzofuran-2-yl)heptan-1-one

To a mixture of 5-methoxy-3-methyl-1-benzofuran (1.87 g) synthesized in Example A104(2), heptanoyl chloride (2.14 mL) and nitromethane (20 mL) was added aluminum chloride (3.07 g), and the mixture was stirred overnight at room temperature. Water was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was

washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (7% ethyl acetate/hexane) to give the title object compound (2.34 g, 74%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 - 0.95 (m, 3 H), 1.24 - 1.48 (m, 6 H), 1.67 - 1.82 (m, 2 H), 2.57 (s, 3 H), 2.96 (t, J=7.4 Hz, 2 H), 3.87 (s, 3 H), 7.00 (d, J=2.6 Hz, 1 H), 7.07 (dd, J=9.1, 2.6 Hz, 1 H), 7.38 (d, J=9.1 Hz, 1 H).

[1274]

(2) methyl 4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)heptyl]amino}benzoate

To a mixture of 1-(5-methoxy-3-methyl-1-benzofuran-2-yl)heptan-1-one (1.18 g) synthesized above, methyl 4-aminobenzoate (715 mg), triethylamine (4.79 mL) and methylene chloride (20 mL) was added titanium (IV) chloride (566 µL), and the mixture was stirred under argon atmosphere overnight at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, methylene chloride was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (20 mL) of the obtained oil in tetrahydrofuran were added acetic acid (1.23 mL) and sodium cyanoborohydride (540 mg), and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 20% ethyl acetate/hexane) to give the title object compound (1.17 g, 66%) as a pale-brown oil

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.82 - 0.88 (m, 3 H), 1.18 - 1.40

(m, 8 H), 1.88 - 2.03 (m, 2 H), 2.24 (s, 3 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 4.51 (d, J=7.7 Hz, 1 H), 4.58 - 4.68 (m, 1 H), 6.56 (d, J=8.8 Hz, 2 H), 6.82 (dd, J=8.8, 2.5 Hz, 1 H), 6.87 (d, J=2.5 Hz, 1 H), 7.25 (d, J=8.8 Hz, 1 H), 7.80 (d, J=8.8 Hz, 2 H).

[1275]

(3) 4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)heptyl]amino}benzoic acid

To a mixture of methyl 4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)heptyl]amino}benzoate (1.17 g) synthesized above, tetrahydrofuran (20 mL) and ethanol (20 mL) was added 1N aqueous sodium hydroxide solution (20.0 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (20.0 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (1.02 g, 90%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.80 - 0.92 (m, 3 H), 1.16 - 1.44 (m, 8 H), 1.90 - 2.03 (m, 2 H), 2.25 (s, 3 H), 3.84 (s, 3 H), 4.65 (t, J=7.3 Hz, 1 H), 6.58 (d, J=8.8 Hz, 2 H), 6.84 (dd, J=8.9, 2.5 Hz, 1 H), 6.89 (d, J=2.5 Hz, 1 H), 7.26 (d, J=8.9 Hz, 1 H), 7.87 (d, J=8.8 Hz, 2 H).

[1276]

(4) ethyl 3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)heptyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)heptyl]amino}benzoic acid (300 mg) synthesized above, β-alanine ethyl ester hydrochloride (175 mg), 1-hydroxybenzotriazole monohydrate (175 mg), triethylamine (318 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (219 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted

with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 100% ethyl acetate/hexane) to give the title object compound (320 mg, 85%) as a colorless oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.81 - 0.90 (m, 3 H), 1.17 - 1.44 (m, 11 H), 1.89 - 2.00 (m, 2 H), 2.24 (s, 3 H), 2.58 (t, J=6.0 Hz, 2 H), 3.66 (q, J=6.0 Hz, 2 H), 3.83 (s, 3 H), 4.14 (q, J=7.1 Hz, 2 H), 4.37 - 4.44 (m, 1 H), 4.55 - 4.66 (m, 1 H), 6.53 - 6.64 (m, 3 H), 6.82 (dd, J=8.8, 2.4 Hz, 1 H), 6.87 (d, J=2.4 Hz, 1 H), 7.24 (d, J=8.8 Hz, 1 H), 7.55 (d, J=8.8 Hz, 2 H).

[1277]

(5)3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)heptyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)heptyl]amino}phenyl)carbonyl]amino}propanoate (320 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 3 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (213 mg, 71%) as a pale-brown solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 (t, J=6.8 Hz, 3 H), 1.16 - 1.43 (m, 8 H), 1.85 - 2.03 (m, 2 H), 2.23 (s, 3 H), 2.63 (t, J=5.8 Hz, 2 H), 3.59 - 3.69 (m, 2 H), 3.83 (s, 3 H), 4.60 (t, J=7.3 Hz, 1 H), 6.56 (d, J=8.9 Hz, 2 H), 6.64 (t, J=6.1 Hz, 1 H), 6.82 (dd, J=8.9, 2.5 Hz, 1 H), 6.88 (d, J=2.5 Hz, 1 H), 7.23 - 7.27 (m, 1 H), 7.53 (d, J=8.9 Hz, 2 H).

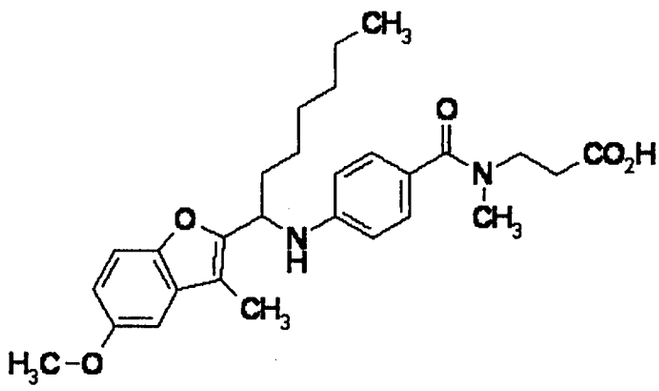
[1278]

Example A119

3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-

yl)heptyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1279]



[1280]

(1) ethyl 3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)heptyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)heptyl]amino}benzoic acid (300 mg) synthesized in Example A118(3), ethyl 3-(methylamino)propanoate (150 mg), 1-hydroxybenzotriazole monohydrate (175 mg), triethylamine (318 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (219 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (289 mg, 75%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 (t, J=6.9 Hz, 3 H), 1.17 - 1.45 (m, 11 H), 1.88 - 2.01 (m, 2 H), 2.24 (s, 3 H), 2.61 (t, J=7.0 Hz, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.0 Hz, 2 H), 3.84 (s, 3 H), 4.11 (q, J=7.1 Hz, 2 H), 4.23 - 4.37 (m, 1 H), 4.54 - 4.63 (m, 1 H), 6.56 (d, J=8.8 Hz, 2 H), 6.82 (dd, J=8.8, 2.4 Hz, 1 H), 6.88 (d, J=2.4 Hz, 1 H), 7.22 (d, J=8.8 Hz, 2 H),

7.25 (d, J=8.8 Hz, 1 H).

[1281]

(2)3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)heptyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)heptyl]amino}phenyl)carbonyl](methyl)amino}propanoate (289 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (153 mg, 56%) as a pale-yellow solid.

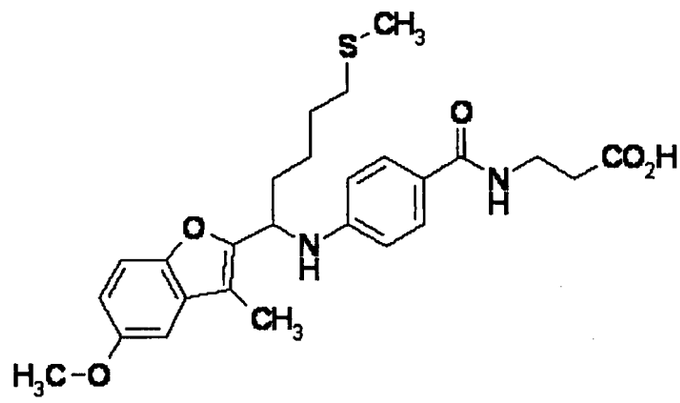
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 (t, J=6.6 Hz, 3 H), 1.16 - 1.44 (m, 8 H), 1.86 - 2.02 (m, 2 H), 2.24 (s, 3 H), 2.64 (t, J=6.6 Hz, 2 H), 3.02 (s, 3 H), 3.69 (t, J=6.6 Hz, 2 H), 3.84 (s, 3 H), 4.59 (t, J=7.3 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.83 (dd, J=8.8, 2.5 Hz, 1 H), 6.89 (d, J=2.5 Hz, 1 H), 7.20 - 7.29 (m, 3 H).

[1282]

Example A120

3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentyl]amino}phenyl)carbonyl]amino}propanoic acid

[1283]



[1284]

(1)5-chloro-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentan-1-one

To a mixture of 5-methoxy-3-methyl-1-benzofuran (2.00 g) synthesized in Example A104(2) above, 5-chlorovaleryl chloride (1.74 mL) and nitromethane (40 mL) was added aluminum chloride (2.47 g) at 0°C, and the mixture was stirred for 2 hr. Water was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% ethyl acetate/hexane) to give the title object compound (2.63 g, 76%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.83 - 1.97 (m, 4 H), 2.58 (s, 3 H), 2.98 - 3.05 (m, 2 H), 3.56 - 3.63 (m, 2 H), 3.87 (s, 3 H), 7.00 (d, J=2.7 Hz, 1 H), 7.08 (dd, J=9.0, 2.7 Hz, 1 H), 7.38 (d, J=9.0 Hz, 1 H).

[1285]

(2)1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentan-1-one

To a mixture of 5-chloro-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentan-1-one (1.30 g) synthesized above, methanol (15 mL) and tetrahydrofuran (15 mL) was added a 15% aqueous solution (4.33 mL) of sodium methanethiolate, and the mixture was stirred at room temperature for 1 hr and at 50°C for 1 hr. Sodium methanethiolate (325 mg) was additionally added and the mixture was stirred at 50°C for 1 hr. Sodium methanethiolate (325 mg) was additionally added again, and the mixture was stirred at 50°C for 1 hr. Water was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with hexane to give

the title object compound (492 mg, 36%) as a yellow solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.64 - 1.79 (m, 2 H), 1.79 - 1.92 (m, 2 H), 2.11 (s, 3 H), 2.51 - 2.62 (m, 5 H), 3.00 (t, J=7.3 Hz, 2 H), 3.87 (s, 3 H), 7.00 (d, J=2.5 Hz, 1 H), 7.08 (dd, J=9.1, 2.5 Hz, 1 H), 7.38 (d, J=9.1 Hz, 1 H).

[1286]

(3) methyl 4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentyl]amino}benzoate

To a mixture of 1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentan-1-one (658 mg) synthesized above, methyl 4-aminobenzoate (375 mg), triethylamine (2.50 mL) and methylene chloride (10 mL) was added a 1.0M solution (2.70 mL) of titanium (IV) chloride in methylene chloride at 0°C, and the mixture was stirred under argon atmosphere at room temperature for 3.5 days. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, methylene chloride was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (10 mL) of the obtained oil in tetrahydrofuran were added acetic acid (647 µL) and sodium cyanoborohydride (283 mg), and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 50% ethyl acetate/hexane) to give the title object compound (645 mg, 67%) as a brown oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 - 1.71 (m, 4 H), 1.91 - 2.08 (m, 5 H), 2.25 (s, 3 H), 2.46 (t, J=7.3 Hz, 2 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 4.52 (d, J=8.0 Hz, 1 H), 4.59 - 4.70 (m, 1 H), 6.57 (d, J=8.8 Hz, 2 H), 6.83 (dd, J=8.7, 2.5 Hz, 1 H), 6.87 (d, J=2.5 Hz, 1 H), 7.25 (d, J=8.7 Hz, 1 H), 7.80 (d,

557

J=8.8 Hz, 2 H).

[1287]

(4)4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentyl]amino}benzoic acid

To a mixture of methyl 4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentyl]amino}benzoate (1.01 g) synthesized above, tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N aqueous sodium hydroxide solution (10.0 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (10.0 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (915 mg, 94%) as a brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.29 - 1.70 (m, 4 H), 1.93 - 2.09 (m, 5 H), 2.25 (s, 3 H), 2.46 (t, J=7.3 Hz, 2 H), 3.83 (s, 3 H), 4.65 (t, J=7.3 Hz, 1 H), 6.57 (d, J=8.8 Hz, 2 H), 6.83 (dd, J=8.8, 2.5 Hz, 1 H), 6.88 (d, J=2.5 Hz, 1 H), 7.25 (d, J=8.8 Hz, 1 H), 7.86 (d, J=8.8 Hz, 2 H).

[1288]

(5) ethyl 3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentyl]amino}benzoic acid (450 mg) synthesized above, β-alanine ethyl ester hydrochloride (252 mg), 1-hydroxybenzotriazole monohydrate (251 mg), triethylamine (456 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (314 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (518 mg, 93%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.25 (t, J=7.1 Hz, 3 H), 1.31 - 1.72 (m, 4 H), 1.91 - 2.10 (m, 5 H), 2.25 (s, 3 H), 2.42 - 2.50 (m, 2 H), 2.59 (t, J=5.8 Hz, 2 H), 3.61 - 3.71 (m, 2 H), 3.84 (s, 3 H), 4.07 - 4.19 (m, 2 H), 4.38 - 4.45 (m, 1 H), 4.57 - 4.68 (m, 1 H), 6.54 - 6.66 (m, 3 H), 6.83 (dd, J=8.7, 2.5 Hz, 1 H), 6.88 (d, J=2.5 Hz, 1 H), 7.25 (d, J=8.7 Hz, 1 H), 7.56 (d, J=8.8 Hz, 2 H).

[1289]

(6)3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentyl]amino}phenyl)carbonyl]amino}propanoate (253 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 3 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (133 mg, 56%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 - 1.69 (m, 4 H), 1.90 - 2.04 (m, 2 H), 2.05 (s, 3 H), 2.24 (s, 3 H), 2.41 - 2.50 (m, 2 H), 2.63 (t, J=5.8 Hz, 2 H), 3.59 - 3.69 (m, 2 H), 3.83 (s, 3 H), 4.62 (t, J=7.3 Hz, 1 H), 6.57 (d, J=8.7 Hz, 2 H), 6.65 (t, J=5.9 Hz, 1 H), 6.83 (dd, J=8.8, 2.5 Hz, 1 H), 6.88 (d, J=2.5 Hz, 1 H), 7.22 - 7.28 (m, 1 H), 7.54 (d, J=8.7 Hz, 2 H).

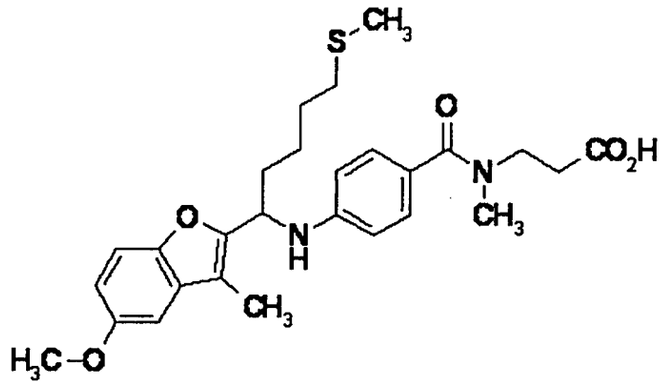
[1290]

Example A121

3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentyl]amino}phenyl)carbonyl](methyl)amino}-

propanoic acid

[1291]



[1292]

(1) ethyl 3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentyl]amino}phenyl)carbonyl](methyl)amino}-propanoate

To a mixture of 4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentyl]amino}benzoic acid (460 mg) synthesized in Example A120(4), ethyl 3-(methylamino)propanoate (219 mg), 1-hydroxybenzotriazole monohydrate (256 mg), triethylamine (464 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (320 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 50% ethyl acetate/hexane) to give the title object compound (514 mg, 88%) as a pale-brown oil

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.23 (t, J=7.1 Hz, 3 H), 1.30 - 1.73 (m, 4 H), 1.88 - 2.10 (m, 5 H), 2.24 (s, 3 H), 2.41 - 2.50 (m, 2 H), 2.55 - 2.67 (m, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.3 Hz, 2 H), 3.84 (s, 3 H), 4.11 (q, J=7.1 Hz, 2 H), 4.27 -

4.35 (m, 1 H), 4.54 - 4.65 (m, 1 H), 6.57 (d, J=8.8 Hz, 2 H), 6.83 (dd, J=8.8, 2.6 Hz, 1 H), 6.88 (d, J=2.6 Hz, 1 H), 7.18 - 7.30 (m, 3 H).

[1293]

(2)3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

To a mixture of ethyl 3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (251 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 3 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (74.8 mg, 33%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.30 - 1.69 (m, 4 H), 1.90 - 2.05 (m, 2 H), 2.06 (s, 3 H), 2.24 (s, 3 H), 2.46 (t, J=6.8 Hz, 2 H), 2.66 (t, J=6.6 Hz, 2 H), 3.03 (s, 3 H), 3.70 (t, J=6.6 Hz, 2 H), 3.84 (s, 3 H), 4.60 (t, J=7.3 Hz, 1 H), 6.57 (d, J=8.9 Hz, 2 H), 6.84 (dd, J=8.9, 2.5 Hz, 1 H), 6.89 (d, J=2.5 Hz, 1 H), 7.21 - 7.30 (m, 3 H).

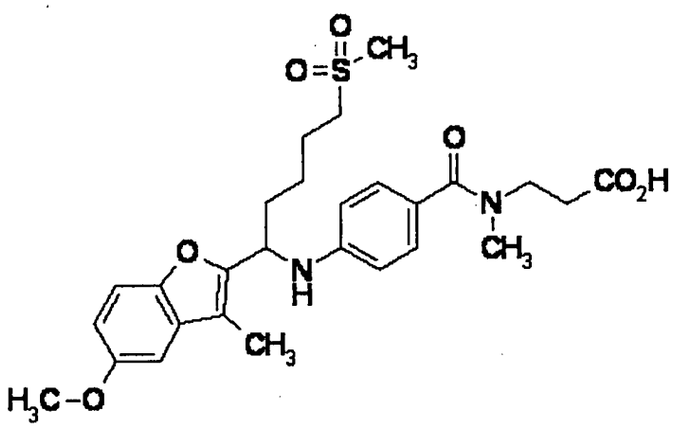
[1294]

Example A122

3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[1295]

561



[1296]

(1) ethyl 3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfonyl)pentyl]amino}phenyl)carbonyl](methyl)amino}-propanoate

To a solution (10 mL) of ethyl 3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfanyl)pentyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (263 mg) synthesized in Example A121(1) in acetone was added m-chloroperbenzoic acid (water-containing, purity 69-75%)(344 mg) at 0°C, and the mixture was stirred overnight at room temperature. Saturated aqueous sodium sulfite solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane), then by NH silica gel column chromatography (ethyl acetate) to give the title object compound (104 mg, 37%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.24 (t, J=7.1 Hz, 3 H), 1.34 - 1.69 (m, 2 H), 1.76 - 2.14 (m, 4 H), 2.24 (s, 3 H), 2.62 (t, J=6.9 Hz, 2 H), 2.85 (s, 3 H), 2.97 (t, J=8.0 Hz, 2 H), 3.02 (s, 3 H), 3.71 (t, J=6.9 Hz, 2 H), 3.84 (s, 3 H), 4.12 (q, J=7.1 Hz, 2 H), 4.30 (d, J=8.0 Hz, 1 H), 4.57 - 4.68 (m, 1 H),

6.58 (d, J=8.7 Hz, 2 H), 6.85 (dd, J=8.7, 2.5 Hz, 1 H), 6.89 (d, J=2.5 Hz, 1 H), 7.19 - 7.31 (m, 3 H).

[1297]

(2)3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfonyl)pentyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

To a mixture of ethyl 3-{[(4-{[1-(5-methoxy-3-methyl-1-benzofuran-2-yl)-5-(methylsulfonyl)pentyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (104 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (52.7 mg, 53%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.34 - 1.69 (m, 2 H), 1.76 - 2.13 (m, 4 H), 2.23 (s, 3 H), 2.66 (t, J=6.4 Hz, 2 H), 2.85 (s, 3 H), 2.96 (t, J=7.8 Hz, 2 H), 3.04 (s, 3 H), 3.70 (t, J=6.4 Hz, 2 H), 3.84 (s, 3 H), 4.59 - 4.66 (m, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 6.85 (dd, J=9.1, 2.5 Hz, 1 H), 6.89 (d, J=2.5 Hz, 1 H), 7.21 - 7.30 (m, 3 H).

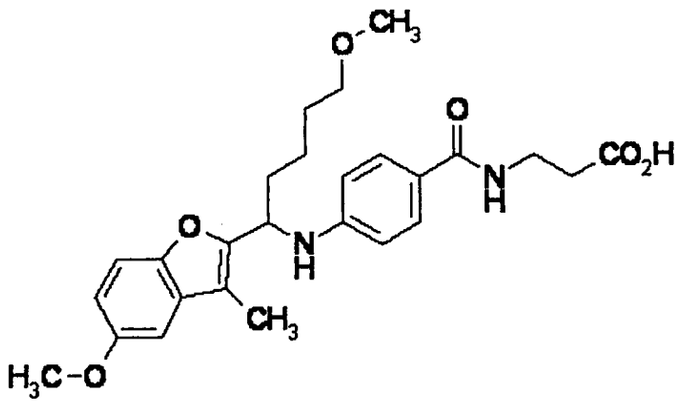
[1298]

Example A123

3-{[(4-{[5-methoxy-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentyl]amino}phenyl)carbonyl]amino}propanoic acid

[1299]

563



[1300]

(1) 5-methoxy-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentan-1-one

To a solution (20 mL) of 5-chloro-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentan-1-one (1.93 g) synthesized in Example A120(1) in methanol were added sodium iodide (1.54 g) and sodium methoxide (1.86 g), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 20% ethyl acetate/hexane) to give the title object compound (797 mg, 42%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.62 - 1.75 (m, 2 H), 1.76 - 1.89 (m, 2 H), 2.58 (s, 3 H), 3.00 (t, J=7.3 Hz, 2 H), 3.33 (s, 3 H), 3.43 (t, J=6.3 Hz, 2 H), 3.87 (s, 3 H), 7.00 (d, J=2.4 Hz, 1 H), 7.07 (dd, J=9.0, 2.4 Hz, 1 H), 7.38 (d, J=9.0 Hz, 1 H).

[1301]

(2) methyl 4-{[5-methoxy-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentyl]amino}benzoate

To a mixture of 5-methoxy-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentan-1-one (797 mg) synthesized above, methyl 4-aminobenzoate (479 mg), triethylamine (3.21 mL) and methylene chloride (10 mL) was added a 1.0M solution (3.46 mL)

of titanium (IV) chloride in methylene chloride at 0°C, and the mixture was stirred under argon atmosphere at room temperature for 3.5 days. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (10 mL) of the obtained oil in tetrahydrofuran were added acetic acid (824 µL) and sodium cyanoborohydride (362 mg), and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 40% ethyl acetate/hexane) to give the title object compound (1.07 g, 90%) as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.27 - 1.67 (m, 4 H), 1.91 - 2.08 (m, 2 H), 2.24 (s, 3 H), 3.30 (s, 3 H), 3.31 - 3.37 (m, 2 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 4.51 - 4.56 (m, 1 H), 4.60 - 4.69 (m, 1 H), 6.56 (d, J=8.8 Hz, 2 H), 6.83 (dd, J=8.8, 2.5 Hz, 1 H), 6.87 (d, J=2.5 Hz, 1 H), 7.25 (d, J=8.8 Hz, 1 H), 7.80 (d, J=8.8 Hz, 2 H).

[1302]

(3)4-{[5-methoxy-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentyl]amino}benzoic acid

To a mixture of methyl 4-{[5-methoxy-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentyl]amino}benzoate (1.07 g) synthesized above, tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N aqueous sodium hydroxide solution (10.0 mL), and the mixture was stirred with heating under reflux for 1 day, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (10.0 mL) was added at 0°C. The resulting precipitate was collected by

filtration to give the title object compound (875 mg, 85%) as a brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.26 - 1.68 (m, 4 H), 1.90 - 2.10 (m, 2 H), 2.25 (s, 3 H), 3.30 (s, 3 H), 3.35 (t, J=6.5 Hz, 2 H), 3.84 (s, 3 H), 4.66 (t, J=7.3 Hz, 1 H), 6.58 (d, J=8.8 Hz, 2 H), 6.84 (dd, J=8.9, 2.5 Hz, 1 H), 6.89 (d, J=2.5 Hz, 1 H), 7.26 (d, J=8.9 Hz, 1 H), 7.86 (d, J=8.8 Hz, 2 H).

[1303]

(4) ethyl 3-{[(4-{[5-methoxy-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[5-methoxy-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentyl]amino}benzoic acid (400 mg) synthesized above, β-alanine ethyl ester hydrochloride (234 mg), 1-hydroxybenzotriazole monohydrate (233 mg), triethylamine (422 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (291 mg), and the mixture was stirred at room temperature for 2.5 days. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (40 - 80% ethyl acetate/hexane) to give the title object compound (489 mg, 97%) as a pale-brown oil

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.25 (t, J=7.1 Hz, 3 H), 1.30 - 1.69 (m, 4 H), 1.88 - 2.08 (m, 2 H), 2.24 (s, 3 H), 2.55 - 2.62 (m, 2 H), 3.30 (s, 3 H), 3.34 (t, J=6.7 Hz, 2 H), 3.62 - 3.70 (m, 2 H), 3.83 (s, 3 H), 4.14 (q, J=7.1 Hz, 2 H), 4.39 - 4.47 (m, 1 H), 4.57 - 4.68 (m, 1 H), 6.54 - 6.64 (m, 3 H), 6.82 (dd, J=8.8, 2.4 Hz, 1 H), 6.87 (d, J=2.4 Hz, 1 H), 7.24 (d, J=8.8 Hz, 1 H), 7.55 (d, J=8.8 Hz, 2 H).

[1304]

(5)3-{[(4-{[5-methoxy-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentyl]amino}phenyl)carbonyl]amino}propanoic acid

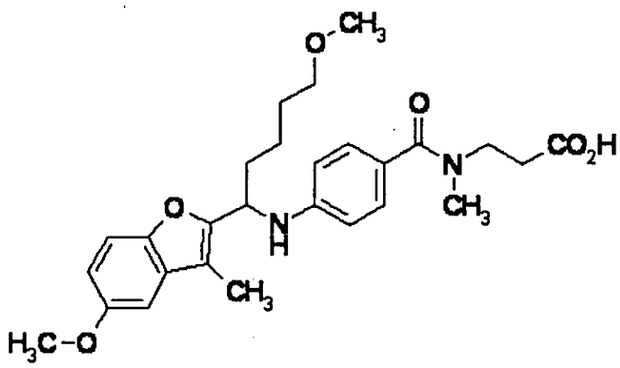
To a mixture of ethyl 3-{[(4-{[5-methoxy-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentyl]amino}phenyl)carbonyl]amino}propanoate (489 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 3 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration, and the obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (453 mg, 98%) as a pale-brown solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.27 - 1.67 (m, 4 H), 1.91 - 2.03 (m, 2 H), 2.23 (s, 3 H), 2.63 (t, J=5.7 Hz, 2 H), 3.30 (s, 3 H), 3.35 (td, J=6.3, 1.2 Hz, 2 H), 3.60 - 3.69 (m, 2 H), 3.83 (s, 3 H), 4.61 (t, J=7.2 Hz, 1 H), 6.56 (d, J=8.8 Hz, 2 H), 6.66 (t, J=6.0 Hz, 1 H), 6.82 (dd, J=8.9, 2.5 Hz, 1 H), 6.87 (d, J=2.5 Hz, 1 H), 7.22 - 7.27 (m, 1 H), 7.54 (d, J=8.8 Hz, 2 H).

[1305]

Example A124

3-{[(4-{[5-methoxy-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1306]



[1307]

(1) ethyl 3-{[(4-{[5-methoxy-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[5-methoxy-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentyl]amino}benzoic acid (400 mg) synthesized in Example A123(3), ethyl 3-(methylamino)propanoate (199 mg), 1-hydroxybenzotriazole monohydrate (233 mg), triethylamine (422 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (291 mg), and the mixture was stirred at room temperature for 2.5 days. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (40 - 80% ethyl acetate/hexane) to give the title object compound (460 mg, 89%) as a pale-yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.24 (t, J=7.1 Hz, 3 H), 1.30 - 1.67 (m, 4 H), 1.88 - 2.06 (m, 2 H), 2.24 (s, 3 H), 2.62 (t, J=7.0 Hz, 2 H), 3.02 (s, 3 H), 3.30 (s, 3 H), 3.35 (t, J=6.3 Hz, 2 H), 3.71 (t, J=7.0 Hz, 2 H), 3.84 (s, 3 H), 4.12 (q, J=7.1 Hz, 2 H), 4.27 - 4.36 (m, 1 H), 4.55 - 4.66 (m, 1 H), 6.57 (d, J=8.8 Hz, 2 H), 6.83 (dd, J=8.8, 2.5 Hz, 1 H), 6.88 (d, J=2.5 Hz, 1 H), 7.18 - 7.28 (m, 3 H).

[1308]

(2)3-{[(4-{[5-methoxy-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[5-methoxy-1-(5-methoxy-3-methyl-1-benzofuran-2-yl)pentyl]amino}phenyl)carbonyl](methyl)amino}propanoate (460 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred overnight at room temperature, and concentrated under reduced pressure. The residue was dissolved

in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (428 mg, 99%) as a pale-yellow solid.

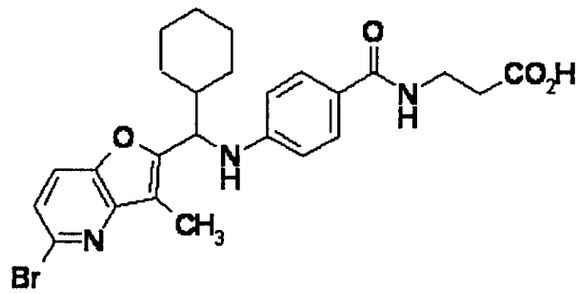
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.27 - 1.67 (m, 4 H), 1.88 - 2.06 (m, 2 H), 2.23 (s, 3 H), 2.67 (t, J=6.6 Hz, 2 H), 3.04 (s, 3 H), 3.30 (s, 3 H), 3.35 (td, J=6.4, 1.0 Hz, 2 H), 3.70 (t, J=6.6 Hz, 2 H), 3.84 (s, 3 H), 4.61 (t, J=7.2 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.83 (dd, J=8.8, 2.4 Hz, 1 H), 6.88 (d, J=2.4 Hz, 1 H), 7.21 - 7.30 (m, 3 H).

[1309]

Example A125

3-{[(4-{[(5-bromo-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1310]




[1311]

(1) 3-(benzyloxy)-6-bromopyridine-2-carbonitrile

To a mixture of 2-cyano-3-hydroxypyridine (10.0 g), water (40 mL) and acetonitrile (200 mL) was added N-bromosuccinimide (17.8 g) at 0°C, and the mixture was stirred at 0°C for 2 hr, and at room temperature for 1 hr. Ethyl acetate was added to the reaction mixture. The solution was washed with water and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a white solid. To a solution (200 mL) of the obtained solid in acetone were added benzyl bromide (11.9 mL) and potassium carbonate (23.1

g), and the mixture was stirred overnight with heating under reflux. Insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was washed with methanol and toluene to give the title object compound (3.17 g, 13%) as a white solid.

$^1$H NMR (300 MHz, DMSO-d) δ ppm 5.36 (s, 2 H), 7.32 - 7.50 (m, 5 H), 7.87 (d, J=9.1 Hz, 1 H), 7.96 (d, J=9.1 Hz, 1 H).

[1312]

(2)1-[3-(benzyloxy)-6-bromopyridin-2-yl]ethanone

To a solution (40 mL) of 3-(benzyloxy)-6-bromopyridine-2-carbonitrile (4.00 g) synthesized above in tetrahydrofuran was added a 1.0M solution (27.6 mL) of methylmagnesium bromide in tetrahydrofuran at 0°C, and the mixture was stirred at room temperature for 5 hr. A 1.0 M solution (13.8 mL) of methylmagnesium bromide in tetrahydrofuran was additionally added, and the mixture was further stirred at room temperature for 1 hr, then 1N hydrochloric acid (80 mL) was added. The mixture was stirred overnight at room temperature, 1N aqueous sodium hydroxide solution (100 mL) was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 - 90% ethyl acetate/hexane) to give the title object compound (1.45 g, 34%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.65 (s, 3 H), 5.18 (s, 2 H), 7.25 (d, J=8.5 Hz, 1 H), 7.28 - 7.46 (m, 5 H), 7.48 (d, J=8.5 Hz, 1 H).

[1313]

(3)1-(6-bromo-3-hydroxypyridin-2-yl)ethanone

To a suspension (30 mL) of aluminum chloride (3.96 g) in toluene was added trimethylammonium chloride (1.32 g), and the mixture was stirred under argon atmosphere at room temperature for 1 hr. A solution (30 mL) of 1-[3-(benzyloxy)-6-bromopyridin-2-yl]ethanone (2.81 g) synthesized above in

toluene was added to the mixture, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated under reduced pressure, saturated aqueous Rochelle salt solution was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 5% ethyl acetate/hexane) to give the title object compound (1.64 g, 83%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.74 (s, 3 H), 7.23 (d, J=8.8 Hz, 1 H), 7.52 (d, J=8.8 Hz, 1 H), 11.77 (s, 1 H).

[1314]

(4) (5-bromo-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methanone

To a mixture of 1-(6-bromo-3-hydroxypyridin-2-yl)ethanone (1.64 g) synthesized above, 2-bromo-1-cyclohexylethanone (2.34 g) synthesized in Example A51(1) and N,N-dimethylformamide (20 mL) was added potassium carbonate (3.15 g), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title object compound (865 mg, 35%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.19 - 1.54 (m, 5 H), 1.70 - 1.81 (m, 1 H), 1.81 - 2.00 (m, 4 H), 2.63 (s, 3 H), 3.23 - 3.35 (m, 1 H), 7.52 (d, J=8.7 Hz, 1 H), 7.69 (d, J=8.7 Hz, 1 H).

[1315]

(5) methyl 4-{[(5-bromo-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}benzoate

To a mixture of (5-bromo-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methanone (1.46 g) synthesized above, methyl 4-aminobenzoate (753 mg), triethylamine (5.05 mL) and methylene

chloride (15 mL) was added a 1.0M solution (5.44 mL) of titanium (IV) chloride in methylene chloride at 0°C, and the mixture was stirred under argon atmosphere overnight at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (20 mL) of the obtained oil in tetrahydrofuran were added acetic acid (1.30 mL) and sodium cyanoborohydride (569 mg), and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 40% ethyl acetate/hexane) to give the title object compound (1.86 g, 90%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 1.35 (m, 5 H), 1.45 - 1.55 (m, 1 H), 1.63 - 2.00 (m, 4 H), 2.04 - 2.14 (m, 1 H), 2.33 (s, 3 H), 3.82 (s, 3 H), 4.43 - 4.54 (m, 2 H), 6.55 (d, J=9.0 Hz, 2 H), 7.29 (d, J=8.5 Hz, 1 H), 7.48 (d, J=8.5 Hz, 1 H), 7.80 (d, J=9.0 Hz, 2 H).

[1316]

(6)4-{[(5-bromo-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}benzoic acid

To a solution (20 mL) of methyl 4-{[(5-bromo-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}benzoate (1.86 g) synthesized above in tetrahydrofuran was added 2N lithium hydroxide aqueous solution (10.2 mL), and the mixture was stirred with heating under reflux for 2 hr. A 4N aqueous lithium hydroxide solution (5.10 mL) was additionally added, and the mixture was stirred with heating under reflux for 4 hr. A 4N aqueous

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lithium hydroxide solution (5.10 mL) and ethanol (20 mL) were further added, and the mixture was stirred with heating under reflux for 4 hr, and concentrated under reduced pressure. The residue was dissolved in water (40 mL), and 1N hydrochloric acid (61.2 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (1.74 g, 96%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.41 (m, 6 H), 1.54 - 1.81 (m, 3 H), 1.87 - 2.02 (m, 1 H), 2.02 - 2.15 (m, 1 H), 2.27 (s, 3 H), 4.52 - 4.62 (m, 1 H), 6.63 (d, J=8.7 Hz, 2 H), 6.92 (d, J=8.0 Hz, 1 H), 7.43 (d, J=8.7 Hz, 1 H), 7.61 (d, J=8.7 Hz, 2 H), 7.90 (d, J=8.7 Hz, 1 H), 12.01 (br s, 1 H).

[1317]

(7) ethyl 3-{[(4-{[(5-bromo-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[(5-bromo-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}benzoic acid (300 mg) synthesized above, β-alanine ethyl ester hydrochloride (157 mg), 1-hydroxybenzotriazole monohydrate (156 mg), triethylamine (283 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (196 mg) and the mixture was stirred at room temperature for 1.5 days. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20 - 60% ethyl acetate/hexane) to give the title object compound (343 mg, 93%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.37 (m, 8 H), 1.44 - 1.55 (m, 1 H), 1.61 - 1.98 (m, 4 H), 2.02 - 2.13 (m, 1 H), 2.31 (s, 3 H), 2.58 (t, J=5.9 Hz, 2 H), 3.61 - 3.70 (m, 2 H), 4.13 (q, J=7.1 Hz, 2 H), 4.40 - 4.50 (m, 2 H), 6.55 (d, J=8.8 Hz, 2 H),

6.63 (t, J=5.9 Hz, 1 H), 7.27 (d, J=8.5 Hz, 1 H), 7.47 (d, J=8.5 Hz, 1 H), 7.54 (d, J=8.8 Hz, 2 H).

[1318]

(8)3-{[(4-{[(5-bromo-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[(5-bromo-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoate (343 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N lithium hydroxide aqueous solution (1.00 mL), and the mixture was stirred at room temperature for 5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (307 mg, 94%) as a pale-yellow solid.

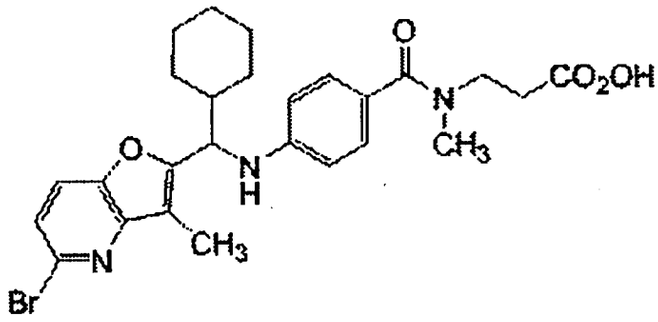
$^1$H NMR (300 MHz, DMSO-d6) δ ppm 0.94 - 1.30 (m, 5 H), 1.30 - 1.42 (m, 1 H), 1.53 - 1.82 (m, 3 H), 1.86 - 2.02 (m, 1 H), 2.03 - 2.15 (m, 1 H), 2.26 (s, 3 H), 2.41 (t, J=7.1 Hz, 2 H), 3.29 - 3.41 (m, 2 H), 4.56 (t, J=8.2 Hz, 1 H), 6.60 (d, J=8.9 Hz, 2 H), 6.66 (d, J=8.2 Hz, 1 H), 7.42 (d, J=8.6 Hz, 1 H), 7.52 (d, J=8.9 Hz, 2 H), 7.89 (d, J=8.6 Hz, 1 H), 8.01 (t, J=5.5 Hz, 1 H).

[1319]

Example A126

3-{[(4-{[(5-bromo-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[1320]



[1321]

(1) ethyl 3-{[(4-{[(5-bromo-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate

To a mixture of 4-{[(5-bromo-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}benzoic acid (300 mg) synthesized in Example A125(6), ethyl 3-(methylamino)propanoate (134 mg), 1-hydroxybenzotriazole monohydrate (156 mg), triethylamine (283 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (196 mg), and the mixture was stirred at room temperature for 1.5 days. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20 - 60% ethyl acetate/hexane) to give the title object compound (317 mg, 84%) as a pale-yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.38 (m, 8 H), 1.44 - 1.55 (m, 1 H), 1.59 - 2.00 (m, 4 H), 2.02 - 2.14 (m, 1 H), 2.32 (s, 3 H), 2.56 - 2.66 (m, 2 H), 3.00 (s, 3 H), 3.69 (t, J=7.0 Hz, 2 H), 4.06 - 4.17 (m, 2 H), 4.27 - 4.34 (m, 1 H), 4.39 - 4.46 (m, 1 H), 6.53 (d, J=8.7 Hz, 2 H), 7.20 (d, J=8.7 Hz, 2 H), 7.28 (d, J=8.5 Hz, 1 H), 7.48 (d, J=8.5 Hz, 1 H).

[1322]

(2)3-{[(4-{[(5-bromo-3-methylfuro[3,2-b]pyridin-2-

yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

To a mixture of ethyl 3-{[(4-{[(5-bromo-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (271 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N lithium hydroxide aqueous solution (1.00 mL), and the mixture was stirred overnight at room temperature, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (271 mg, 90%) as a pale-yellow solid.

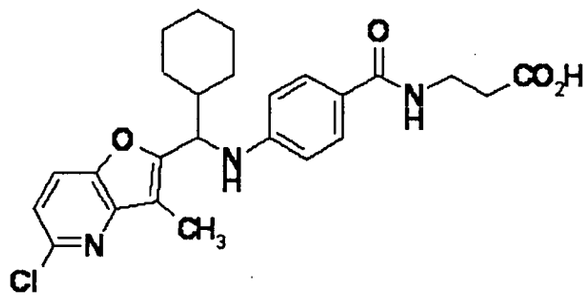
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.37 (m, 5 H), 1.44 - 1.55 (m, 1 H), 1.60 - 1.97 (m, 4 H), 2.03 - 2.14 (m, 1 H), 2.31 (s, 3 H), 2.64 (t, J=6.3 Hz, 2 H), 3.02 (s, 3 H), 3.69 (t, J=6.3 Hz, 2 H), 4.43 (d, J=7.9 Hz, 1 H), 6.54 (d, J=8.6 Hz, 2 H), 7.23 (d, J=8.6 Hz, 2 H), 7.29 (d, J=8.6 Hz, 1 H), 7.49 (d, J=8.6 Hz, 1 H).

[1323]

Example A127

3-{[(4-{[(5-chloro-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1324]




[1325]

(1)3-(benzyloxy)-6-chloro-2-iodopyridine

S76

To an aqueous solution (100 mL) of 2-chloro-5-hydroxypyridine (10.0 g) were added sodium carbonate (16.3 g) and iodine (10.8 g), and the mixture was stirred at room temperature for 5 days. The reaction mixture was acidified to pH=5 with 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a yellow solid. The obtained solid was recrystallized from methanol to give a brown solid. To a solution (200 mL) of the obtained solid in acetone were added benzyl bromide (8.02 mL) and potassium carbonate (15.5 g), and the mixture was stirred overnight with heating under reflux. Insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 30% ethyl acetate/hexane) to give the title object compound (18.4 g, 69%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 5.17 (s, 2 H), 6.97 (d, J=8.4 Hz, 1 H), 7.15 (d, J=8.4 Hz, 1 H), 7.30 - 7.47 (m, 5 H).

[1326]

(2)1-[3-(benzyloxy)-6-chloropyridin-2-yl]ethanol

To a solution (100 mL) of 3-(benzyloxy)-6-chloro-2-iodopyridine (17.4 g) synthesized above in tetrahydrofuran was added a 1.0 M solution (60.2 mL) of isopropylmagnesium bromide in tetrahydrofuran at -45°C, and the mixture was stirred at the same temperature for 1 hr. Acetaldehyde (10.2 mL) was added to the reaction mixture, and the mixture was stirred at -45°C for 30 min then at room temperature for 2 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, tetrahydrofuran was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 30% ethyl acetate/hexane) to give the title object compound (6.82 g,

52%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.46 (d, J=6.6 Hz, 3 H), 3.95 (d, J=7.7 Hz, 1 H), 5.06 - 5.18 (m, 3 H), 7.14 (d, J=8.5 Hz, 1 H), 7.17 (d, J=8.5 Hz, 1 H), 7.31 - 7.44 (m, 5 H).

[1327]

(3)1-[3-(benzyloxy)-6-chloropyridin-2-yl]ethanone

To a mixture of 1-[3-(benzyloxy)-6-chloropyridin-2-yl]ethanol (7.04 g) synthesized above, 4-methylmorpholine N-oxide (6.26 g) and acetonitrile (140 mL) was added tetrapropylammonium perruthenate (938 mg), and the mixture was stirred at room temperature for 3 hr, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 10% ethyl acetate/hexane) to give the title object compound (6.26 g, 90%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.66 (s, 3 H), 5.19 (s, 2 H), 7.27 - 7.47 (m, 7 H).

[1328]

(4)1-(6-chloro-3-hydroxypyridin-2-yl)ethanone

To a suspension (80 mL) of aluminum chloride (14.3 g) in toluene was added trimethylammonium chloride (4.75 g), and the mixture was stirred under argon atmosphere at room temperature for 1 hr. To the mixture was added a solution (80 mL) of 1-[3-(benzyloxy)-6-chloropyridin-2-yl]ethanone (8.66 g) synthesized above in toluene, and the mixture was stirred at room temperature for 4 hr. The reaction mixture was concentrated under reduced pressure, saturated aqueous Rochelle salt solution was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 5% ethyl acetate/hexane) to give the title object compound (4.89 g, 86%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.74 (s, 3 H), 7.31 (d, J=8.8 Hz, 1 H), 7.39 (d, J=8.8 Hz, 1 H), 11.77 (s, 1 H).

[1329]

(5) (5-chloro-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methanone

To a mixture of 1-(6-chloro-3-hydroxypyridin-2-yl)ethanone (4.89 g) synthesized above, 2-bromo-1-cyclohexylethanone (7.01 g) synthesized in Example A51(1) and N,N-dimethylformamide (50 mL) was added potassium carbonate (11.8 g), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title object compound (5.78 g, 73%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.19 - 1.61 (m, 5 H), 1.70 - 1.80 (m, 1 H), 1.81 - 2.01 (m, 4 H), 2.63 (s, 3 H), 3.23 - 3.35 (m, 1 H), 7.39 (d, J=8.7 Hz, 1 H), 7.78 (d, J=8.7 Hz, 1 H).

[1330]

(6) methyl 4-{[(5-chloro-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}benzoate

To a mixture of (5-chloro-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methanone (1.00 g) synthesized above, methyl 4-aminobenzoate (599 mg), triethylamine (4.01 mL) and methylene chloride (10 mL) was added a 1.0M solution (4.32 mL) of titanium (IV) chloride in methylene chloride at 0°C, and the mixture was stirred under argon atmosphere overnight at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (15 mL) of the obtained oil in tetrahydrofuran were added acetic acid (1.03 mL) and sodium cyanoborohydride (452 mg), and the mixture was stirred at room temperature for

2 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 40% ethyl acetate/hexane) to give the title object compound (1.31 g, 81%) as an orange solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 1.37 (m, 5 H), 1.45 - 1.56 (m, 1 H), 1.63 - 1.99 (m, 4 H), 2.03 - 2.14 (m, 1 H), 2.32 (s, 3 H), 3.81 (s, 3 H), 4.43 - 4.56 (m, 2 H), 6.54 (d, J=9.0 Hz, 2 H), 7.14 (d, J=8.5 Hz, 1 H), 7.56 (d, J=8.5 Hz, 1 H), 7.79 (d, J=9.0 Hz, 2 H).

[1331]

(7)4-{[(5-chloro-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}benzoic acid

To a mixture of methyl 4-{[(5-chloro-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}benzoate (1.31 g) synthesized above, ethanol (20 mL) and tetrahydrofuran (20 mL) was added 1N lithium hydroxide aqueous solution (20 mL), and the mixture was stirred with heating under reflux for 3 hr, and concentrated under reduced pressure. The residue was dissolved in water (40 mL), and 1N hydrochloric acid (20 mL) was added at 0°C. The resulting precipitate was collected by filtration and the obtained solid was dissolved in ethyl acetate. The solution was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title object compound (1.21 g, 96%) as a pale-yellow solid.

$^1$H NMR (300 MHz, DMSO-d6) δ ppm 0.96 - 1.42 (m, 6 H), 1.54 - 1.82 (m, 3 H), 1.87 - 2.03 (m, 1 H), 2.04 - 2.16 (m, 1 H), 2.28 (s, 3 H), 4.53 - 4.64 (m, 1 H), 6.64 (d, J=8.9 Hz, 2 H), 6.95 (d, J=7.9 Hz, 1 H), 7.32 (d, J=8.6 Hz, 1 H), 7.62 (d, J=8.9 Hz, 2 H), 7.99 (d, J=8.6 Hz, 1 H), 12.02 (br s, 1 H).

[1332]

(8) ethyl 3-{[(4-{[(5-chloro-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[(5-chloro-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}benzoic acid (300 mg) synthesized above, β-alanine ethyl ester hydrochloride (174 mg), 1-hydroxybenzotriazole monohydrate (173 mg), triethylamine (315 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (217 mg), and the mixture was stirred at room temperature for 2.5 days. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (383 mg, quantitative) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 1.37 (m, 8 H), 1.45 - 1.56 (m, 1 H), 1.61 - 1.99 (m, 4 H), 2.02 - 2.14 (m, 1 H), 2.31 (s, 3 H), 2.54 - 2.62 (m, 2 H), 3.60 - 3.69 (m, 2 H), 4.13 (q, J=7.1 Hz, 2 H), 4.40 - 4.50 (m, 2 H), 6.55 (d, J=8.8 Hz, 2 H), 6.62 (t, J=5.9 Hz, 1 H), 7.14 (d, J=8.5 Hz, 1 H), 7.54 (d, J=8.8 Hz, 2 H), 7.55 (d, J=8.5 Hz, 1 H).

[1333]

(9)3-{[(4-{[(5-chloro-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[(5-chloro-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoate (383 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 2 hr,

and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (328 mg, 93%) as a white solid.

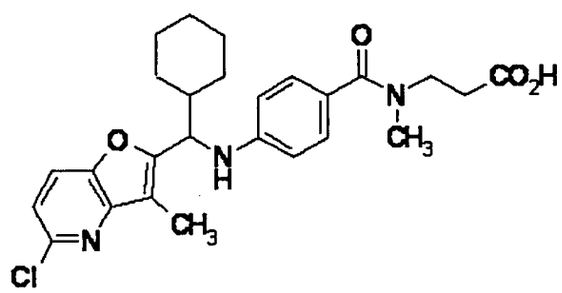
$^1$H NMR (300 MHz, DMSO-d6) δ ppm 0.95 - 1.30 (m, 5 H), 1.30 - 1.41 (m, 1 H), 1.55 - 1.82 (m, 3 H), 1.87 - 2.01 (m, 1 H), 2.04 - 2.16 (m, 1 H), 2.26 (s, 3 H), 2.42 (t, J=7.2 Hz, 2 H), 3.26 - 3.42 (m, 2 H), 4.56 (t, J=8.2 Hz, 1 H), 6.60 (d, J=8.9 Hz, 2 H), 6.68 (d, J=8.2 Hz, 1 H), 7.31 (d, J=8.5 Hz, 1 H), 7.52 (d, J=8.9 Hz, 2 H), 7.93 - 8.06 (m, 2 H).

[1334]

Example A128

3-{[(4-{[(5-chloro-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[1335]



[1336]

(1) ethyl 3-{[(4-{[(5-chloro-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate

To a mixture of 4-{[(5-chloro-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}benzoic acid (300 mg) synthesized in Example A127(7), ethyl 3-(methylamino)propanoate (148 mg), 1-hydroxybenzotriazole monohydrate (173 mg), triethylamine (315 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (217 mg), and

the mixture was stirred at room temperature for 2.5 days. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (332 mg, 86%) as a pale-yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 1.38 (m, 8 H), 1.44 - 1.56 (m, 1 H), 1.61 - 1.99 (m, 4 H), 2.03 - 2.15 (m, 1 H), 2.31 (s, 3 H), 2.61 (t, J=6.9 Hz, 2 H), 3.00 (s, 3 H), 3.69 (t, J=6.9 Hz, 2 H), 4.06 - 4.17 (m, 2 H), 4.29 - 4.36 (m, 1 H), 4.39 - 4.47 (m, 1 H), 6.54 (d, J=8.7 Hz, 2 H), 7.14 (d, J=8.5 Hz, 1 H), 7.21 (d, J=8.7 Hz, 2 H), 7.56 (d, J=8.5 Hz, 1 H).

[1337]

(2)3-{[(4-{[(5-chloro-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

To a mixture of ethyl 3-{[(4-{[(5-chloro-3-methylfuro[3,2-b]pyridin-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (332 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N lithium hydroxide aqueous solution (3.00 mL), and the mixture was stirred overnight at room temperature, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (3.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (278 mg, 89%) as a pale-yellow solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.38 (m, 5 H), 1.44 - 1.56 (m, 1 H), 1.61 - 1.98 (m, 4 H), 2.02 - 2.15 (m, 1 H), 2.31 (s, 3 H), 2.62 (t, J=6.3 Hz, 2 H), 3.00 (s, 3 H), 3.68 (t, J=6.3 Hz, 2 H), 4.43 (d, J=8.0 Hz, 1 H), 6.54 (d, J=8.5 Hz, 2 H), 7.14 (d, J=8.5 Hz, 1 H), 7.22 (d, J=8.5 Hz, 2 H), 7.57 (d,

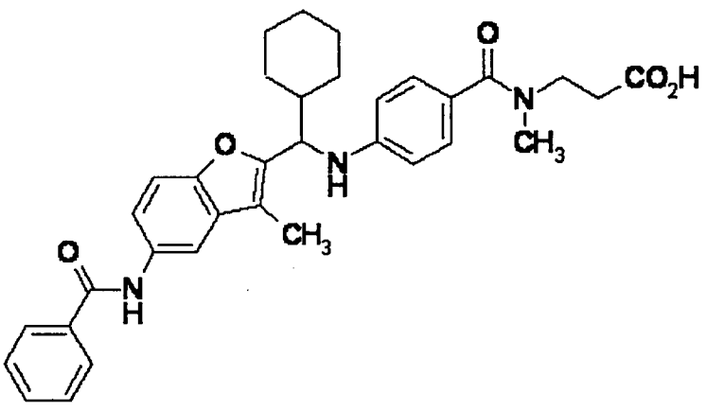
J=8.5 Hz, 1 H).

[1338]

Example A129

3-[({4-[(cyclohexyl{3-methyl-5-[(phenylcarbonyl)amino]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[1339]



[1340]

To a solution (10 mL) of ethyl 3-{[(4-{[(5-amino-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (280 mg) synthesized in Example A110(5) in N,N-dimethylacetamide was added benzoyl chloride (99 µL), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give a pale-red oil. To a mixture of the obtained oil, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N lithium hydroxide aqueous solution (2.00 mL), and the mixture was stirred at room temperature for 5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N

hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (303 mg, 94%) as a white solid.

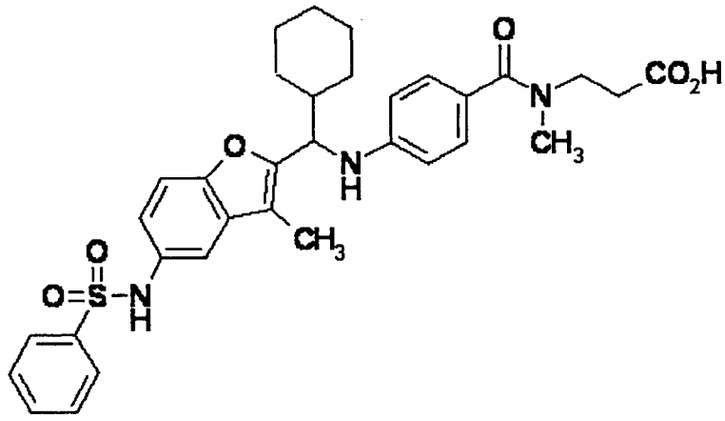
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.38 (m, 5 H), 1.46 - 1.58 (m, 1 H), 1.60 - 1.99 (m, 4 H), 2.03 - 2.16 (m, 1 H), 2.19 (s, 3 H), 2.44 - 2.60 (m, 2 H), 2.96 (s, 3 H), 3.49 - 3.64 (m, 2 H), 4.36 (d, J=8.0 Hz, 1 H), 6.54 (d, J=8.7 Hz, 2 H), 7.13 - 7.33 (m, 4 H), 7.39 - 7.56 (m, 3 H), 7.80 (s, 1 H), 7.85 - 7.92 (m, 2 H), 8.21 (s, 1 H).

[1341]

Example A130

3-[({4-[(cyclohexyl{3-methyl-5-[(phenylsulfonyl)amino]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[1342]



[1343]

(1) ethyl 3-[({4-[(cyclohexyl{3-methyl-5-[(phenylsulfonyl)amino]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate

To a solution (10 mL) of ethyl 3-{[(4-{[(5-amino-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (254 mg) synthesized in Example A110(5) in N,N-dimethylacetamide was added benzenesulfonyl chloride (99 µL), and the mixture was stirred overnight at room temperature.

Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (312 mg, 96%) as a colorless oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 1.34 (m, 8 H), 1.41 - 1.54 (m, 1 H), 1.58 - 1.95 (m, 4 H), 2.04 - 2.12 (m, 1 H), 2.18 (s, 3 H), 2.56 - 2.68 (m, 2 H), 3.02 (s, 3 H), 3.71 (t, J=6.7 Hz, 2 H), 4.12 (q, J=7.1 Hz, 2 H), 4.28 - 4.39 (m, 2 H), 6.51 - 6.58 (m, 3 H), 6.78 (dd, J=8.8, 2.2 Hz, 1 H), 7.14 - 7.24 (m, 4 H), 7.37 - 7.46 (m, 2 H), 7.48 - 7.56 (m, 1 H), 7.68 - 7.74 (m, 2 H).

[1344]

(2)3-[({4-[(cyclohexyl{3-methyl-5-[(phenylsulfonyl)amino]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

To a mixture of ethyl 3-[({4-[(cyclohexyl{3-methyl-5-[(phenylsulfonyl)amino]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate (312 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (240 mg, 80%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.89 - 1.37 (m, 5 H), 1.40 - 1.55 (m, 1 H), 1.58 - 1.97 (m, 4 H), 2.02 - 2.13 (m, 1 H), 2.16 (s, 3 H), 2.62 (t, J=6.1 Hz, 2 H), 3.01 (s, 3 H), 3.68 (t, J=6.1 Hz, 2 H), 4.34 (d, J=8.0 Hz, 1 H), 6.53 (d, J=8.7 Hz, 2 H), 6.79 (dd, J=8.7, 2.3 Hz, 1 H), 6.84 - 6.98 (m, 1 H), 7.11 - 7.25 (m, 4 H), 7.34 - 7.42 (m, 2 H), 7.45 - 7.53 (m, 1 H),

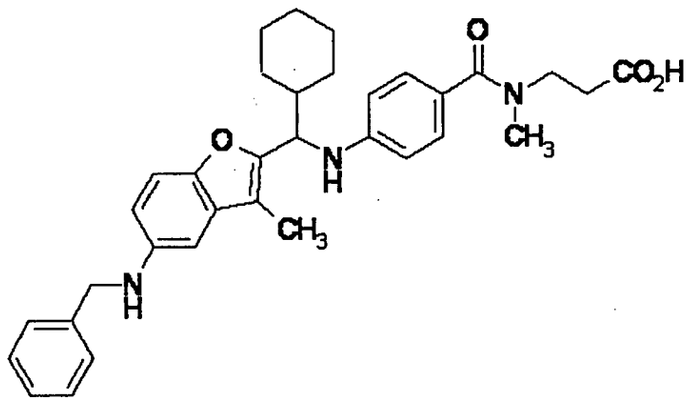
7.67 - 7.74 (m, 2 H).

[1345]

Example A131

3-[{[4-({[5-(benzylamino)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoic acid

[1346]



[1347]

(1) ethyl 3-[{[4-({[5-(benzylamino)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoate

To a mixture of ethyl 3-{[(4-{[(5-amino-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (322 mg) synthesized in Example A110(5), benzaldehyde (100 µL) and ethanol (10 mL) were added acetic acid (56 µL) and sodium cyanoborohydride (61.6 mg), and the mixture was stirred at room temperature for 1.5 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (354 mg, 93%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.37 (m, 8 H), 1.47 - 1.96 (m, 5 H), 2.01 - 2.12 (m, 1 H), 2.17 (s, 3 H), 2.56 - 2.67 (m, 2 H), 3.02 (s, 3 H), 3.66 - 3.77 (m, 3 H), 4.06 - 4.18 (m, 2 H), 4.29 - 4.39 (m, 4 H), 6.51 - 6.64 (m, 4 H), 7.14 - 7.43 (m, 8 H).

[1348]

(2)3-[{[4-({[5-(benzylamino)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoic acid

To a mixture of ethyl 3-[{[4-({[5-(benzylamino)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoate (354 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 1.5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (310 mg, 92%) as a white solid.

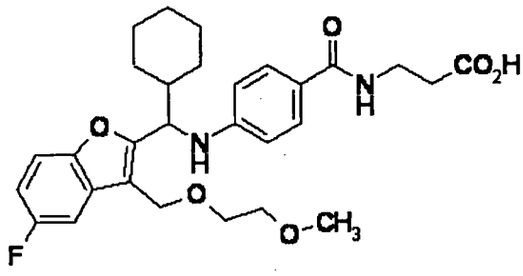
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.34 (m, 5 H), 1.47 - 1.58 (m, 1 H), 1.60 - 1.97 (m, 4 H), 2.01 - 2.12 (m, 1 H), 2.17 (s, 3 H), 2.67 (t, J=6.4 Hz, 2 H), 3.04 (s, 3 H), 3.65 - 3.73 (m, 2 H), 4.30 - 4.36 (m, 3 H), 6.55 (d, J=8.7 Hz, 2 H), 6.59 (dd, J=8.7, 2.7 Hz, 1 H), 6.63 - 6.67 (m, 1 H), 7.17 (d, J=8.7 Hz, 1 H), 7.20 - 7.42 (m, 7 H).

[1349]

Example A132

3-[({4-[(cyclohexyl{5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[1350]



[1351]

(1) methyl 5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-carboxylate

To a solution (25 mL) of 2-methoxyethanol (2.74 mL) in N,N-dimethylformamide was added sodium hydride (60%, oily, 835 mg) at 0°C, and the mixture was stirred at room temperature for 30 min. After stirring, a solution (25 mL) of methyl 3-(bromomethyl)-5-fluoro-1-benzofuran-2-carboxylate (5.00 g) synthesized in Example A47(2) in N,N-dimethylformamide was added at 0°C. The reaction mixture was stirred at 80°C for 5 hr, then saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 40% ethyl acetate/hexane) to give the title object compound (1.54 g, 31%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.40 (s, 3 H), 3.57 - 3.62 (m, 2 H), 3.66 - 3.72 (m, 2 H), 3.99 (s, 3 H), 5.11 (s, 2 H), 7.14 - 7.22 (m, 1 H), 7.45 - 7.51 (m, 1 H), 7.60 - 7.65 (m, 1 H).

[1352]

(2){5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methanol

To a mixture of methyl 5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-carboxylate (1.54 g) synthesized above, calcium chloride (1.21 g), ethanol (15 mL) and tetrahydrofuran (15 mL) was added sodium borohydride (825 mg) at 0°C, and the mixture was stirred at room temperature for

3 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (1.34 g, 97%) as a pale-yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.38 (s, 3 H), 3.55 - 3.60 (m, 2 H), 3.63 - 3.68 (m, 2 H), 4.73 (s, 2 H), 4.76 (br s, 2 H), 6.95 - 7.04 (m, 1 H), 7.17 - 7.23 (m, 1 H), 7.33 - 7.40 (m, 1 H).

[1353]

(3)5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-carbaldehyde

To a mixture of {5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methanol (2.65 g) synthesized above, 4-methylmorpholine N-oxide (2.44 g) and acetonitrile (50 mL) was added tetrapropylammonium perruthenate (366 mg), and the mixture was stirred for 5 hr, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 30% ethyl acetate/hexane) to give the title object compound (1.33 g, 51%) as a yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.41 (s, 3 H), 3.58 - 3.64 (m, 2 H), 3.72 - 3.77 (m, 2 H), 5.07 (s, 2 H), 7.21 - 7.29 (m, 1 H), 7.48 - 7.57 (m, 2 H), 10.09 (s, 1 H).

[1354]

(4)cyclohexyl{5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methanone

To a solution (20 mL) of 5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-carbaldehyde (1.33 g) synthesized above in tetrahydrofuran was added a 1.0M solution (7.91 mL) of cyclohexylmagnesium bromide in tetrahydrofuran at 0°C, and the mixture was stirred for 2 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium

S90

sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 40% ethyl acetate/hexane) to give a pale-yellow oil. To a mixture of the obtained oil, 4-methylmorpholine N-oxide (933 mg) and acetonitrile (20 mL) was added tetrapropylammonium perruthenate (140 mg), and the mixture was stirred overnight at room temperature, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 20% ethyl acetate/hexane) to give the title object compound (881 mg, 50%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.17 - 1.55 (m, 5 H), 1.70 - 1.80 (m, 1 H), 1.80 - 2.01 (m, 4 H), 3.24 - 3.37 (m, 1 H), 3.40 (s, 3 H), 3.57 - 3.63 (m, 2 H), 3.66 - 3.72 (m, 2 H), 5.11 (s, 2 H), 7.14 - 7.23 (m, 1 H), 7.41 - 7.48 (m, 1 H), 7.64 - 7.70 (m, 1 H).

[1355]

(5) methyl 4-[(cyclohexyl{5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methyl)amino]benzoate

To a mixture of cyclohexyl{5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methanone (881 mg) synthesized above, methyl 4-aminobenzoate (440 mg), triethylamine (2.93 mL) and methylene chloride (10 mL) was added a 1.0M solution (3.16 mL) of titanium (IV) chloride in methylene chloride, and the mixture was stirred under argon atmosphere overnight at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown solid. To a solution (10 mL) of the obtained solid in tetrahydrofuran were added acetic acid (301 µL) and sodium cyanoborohydride (331 mg), and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl

acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 40% ethyl acetate/hexane) to give the title object compound (482 mg, 39%) as a brown oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.96 - 1.35 (m, 5 H), 1.41 - 1.51 (m, 1 H), 1.58 - 1.85 (m, 3 H), 1.86 - 2.01 (m, 1 H), 2.01 - 2.13 (m, 1 H), 3.43 (s, 3 H), 3.53 - 3.60 (m, 2 H), 3.60 - 3.67 (m, 2 H), 3.80 (s, 3 H), 4.46 - 4.72 (m, 3 H), 4.99 (d, J=8.8 Hz, 1 H), 6.60 (d, J=9.0 Hz, 2 H), 6.88 - 6.98 (m, 1 H), 7.13 - 7.19 (m, 1 H), 7.27 - 7.34 (m, 1 H), 7.78 (d, J=9.0 Hz, 2 H).

[1356]

(6)4-[(cyclohexyl{5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methyl)amino]benzoic acid

To a mixture of methyl 4-[(cyclohexyl{5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methyl)amino]benzoate (482 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (5.00 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (5.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (437 mg, 93%) as a pale-red solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.99 - 1.35 (m, 5 H), 1.40 - 1.53 (m, 1 H), 1.59 - 1.85 (m, 3 H), 1.86 - 2.14 (m, 2 H), 3.44 (s, 3 H), 3.52 - 3.70 (m, 4 H), 4.49 - 4.73 (m, 3 H), 6.62 (d, J=8.9 Hz, 2 H), 6.91 - 7.00 (m, 1 H), 7.14 - 7.20 (m, 1 H), 7.29 - 7.36 (m, 1 H), 7.84 (d, J=8.9 Hz, 2 H).

[1357]

(7) ethyl 3-[({4-[(cyclohexyl{5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoate

To a mixture of 4-[(cyclohexyl{5-fluoro-3-[(2-

methoxyethoxy)methyl]-1-benzofuran-2-yl}methyl)amino]benzoic acid (200 mg) synthesized above, β-alanine ethyl ester hydrochloride (101 mg), 1-hydroxybenzotriazole monohydrate (101 mg), triethylamine (184 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (126 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (216 mg, 89%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 1.34 (m, 8 H), 1.41 - 1.52 (m, 1 H), 1.60 - 2.01 (m, 4 H), 2.03 - 2.13 (m, 1 H), 2.58 (t, J=5.9 Hz, 2 H), 3.43 (s, 3 H), 3.54 - 3.69 (m, 6 H), 4.13 (q, J=7.1 Hz, 2 H), 4.45 - 4.53 (m, 1 H), 4.57 (d, J=12.1 Hz, 1 H), 4.65 (d, J=12.1 Hz, 1 H), 4.87 (d, J=8.5 Hz, 1 H), 6.56 - 6.65 (m, 3 H), 6.88 - 6.98 (m, 1 H), 7.14 - 7.20 (m, 1 H), 7.28 - 7.34 (m, 1 H), 7.53 (d, J=8.8 Hz, 2 H).

[1358]

(8)3-[({4-[(cyclohexyl{5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

To a mixture of ethyl 3-[({4-[(cyclohexyl{5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoate (216 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 3 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (69.6 mg, 34%) as a pale-

yellow solid.

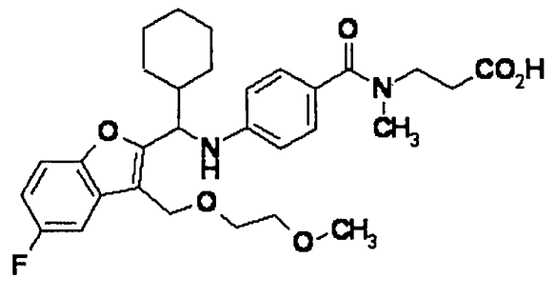
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.99 - 1.35 (m, 5 H), 1.40 - 1.51 (m, 1 H), 1.59 - 1.85 (m, 3 H), 1.84 - 2.00 (m, 1 H), 2.01 - 2.12 (m, 1 H), 2.63 (t, J=5.7 Hz, 2 H), 3.42 (s, 3 H), 3.54 - 3.69 (m, 6 H), 4.49 (d, J=8.3 Hz, 1 H), 4.56 (d, J=12.1 Hz, 1 H), 4.64 (d, J=12.1 Hz, 1 H), 6.53 - 6.67 (m, 3 H), 6.88 - 6.99 (m, 1 H), 7.12 - 7.20 (m, 1 H), 7.27 - 7.34 (m, 1 H), 7.52 (d, J=8.7 Hz, 2 H).

[1359]

Example A133

3-[({4-[(cyclohexyl{5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[1360]



[1361]

(1) ethyl 3-[({4-[(cyclohexyl{5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate

To a mixture of 4-[(cyclohexyl{5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methyl)amino]benzoic acid (200 mg) synthesized in Example A132(6), ethyl 3-(methylamino)propanoate (86.4 mg), 1-hydroxybenzotriazole monohydrate (101 mg), triethylamine (184 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (126 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted

with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (175 mg, 70%) as a pale-brown oil
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 1.37 (m, 8 H), 1.42 - 1.53 (m, 1 H), 1.59 - 2.00 (m, 4 H), 2.03 - 2.14 (m, 1 H), 2.61 (t, J=7.0 Hz, 2 H), 3.01 (s, 3 H), 3.42 (s, 3 H), 3.54 - 3.75 (m, 6 H), 4.11 (q, J=7.1 Hz, 2 H), 4.42 - 4.51 (m, 1 H), 4.59 (d, J=12.1 Hz, 1 H), 4.65 (d, J=12.1 Hz, 1 H), 4.71 (d, J=8.5 Hz, 1 H), 6.59 (d, J=8.8 Hz, 2 H), 6.89 - 6.98 (m, 1 H), 7.16 - 7.23 (m, 3 H), 7.28 - 7.34 (m, 1 H).

[1362]

(2)3-[({4-[(cyclohexyl{5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

To a mixture of ethyl 3-[({4-[(cyclohexyl{5-fluoro-3-[(2-methoxyethoxy)methyl]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate (175 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), 1N hydrochloric acid (1.00 mL) was added at 0°C, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (143 mg, 82%) as a yellow solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.99 - 1.35 (m, 5 H), 1.40 - 1.51 (m, 1 H), 1.60 - 2.00 (m, 4 H), 2.02 - 2.15 (m, 1 H), 2.64 (t, J=6.4 Hz, 2 H), 3.02 (s, 3 H), 3.42 (s, 3 H), 3.54 - 3.75 (m, 6 H), 4.47 (d, J=8.3 Hz, 1 H), 4.59 (d, J=12.3 Hz, 1 H), 4.66 (d, J=12.3 Hz, 1 H), 6.60 (d, J=8.7 Hz, 2 H), 6.89 - 6.99 (m, 1 H), 7.16 - 7.25 (m, 3 H), 7.28 - 7.35 (m, 1 H).

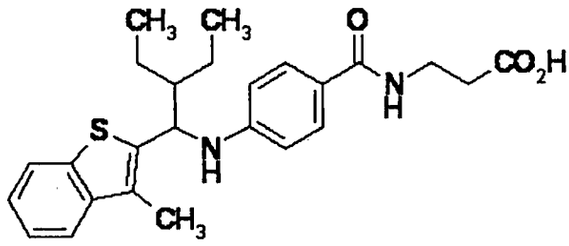
[1363]

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Example A134

3-{[(4-{[2-ethyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}phenyl)carbonyl]amino}propanoic acid

[1364]



[1365]

(1)2-ethyl-1-(3-methyl-1-benzothiophen-2-yl)butan-1-one

To a mixture of 3-methyl-1-benzothiophene (1.00 g), 2-ethylbutyryl chloride (1.02 mL) and nitromethane (10 mL) was added aluminum chloride (1.35 g) at 0°C, and the mixture was stirred for 3 hr. Water was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 10% ethyl acetate/hexane) to give the title object compound (1.65 g, 99%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 (t, J=7.4 Hz, 6 H), 1.51 - 1.67 (m, 2 H), 1.75 - 1.92 (m, 2 H), 2.78 (s, 3 H), 2.97 - 3.08 (m, 1 H), 7.40 - 7.53 (m, 2 H), 7.81 - 7.91 (m, 2 H).

[1366]

(2) methyl 4-{[2-ethyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}benzoate

To a mixture of 2-ethyl-1-(3-methyl-1-benzothiophen-2-yl)butan-1-one (1.65 g) synthesized above, methyl 4-aminobenzoate (1.15 g), triethylamine (7.47 mL) and methylene chloride (15 mL) was added a 1.0M solution (8.04 mL) of titanium (IV) chloride in methylene chloride, and the mixture was stirred under argon atmosphere overnight at room temperature. Saturated aqueous sodium hydrogen carbonate

solution was added to quench the reaction, methylene chloride was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a mixture of the obtained oil, methyl 4-aminobenzoate (506 mg), triethylamine (7.47 mL) and methylene chloride (30 mL) was added titanium (IV) chloride (882 μL), and the mixture was stirred under argon atmosphere overnight at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (30 mL) of the obtained oil in tetrahydrofuran were added acetic acid (797 μL) and sodium cyanoborohydride (842 mg) and the mixture was stirred at room temperature stirred for 1.5 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, the organic solvent was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 - 40% ethyl acetate/hexane) to give the title object compound (580 mg, 23%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 - 0.99 (m, 6 H), 1.33 - 1.56 (m, 3 H), 1.67 - 1.84 (m, 2 H), 2.46 (s, 3 H), 3.79 (s, 3 H), 4.45 (d, J=6.6 Hz, 1 H), 4.81 - 4.89 (m, 1 H), 6.52 (d, J=9.0 Hz, 2 H), 7.22 - 7.29 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.61 - 7.66 (m, 1 H), 7.67 - 7.71 (m, 1 H), 7.77 (d, J=9.0 Hz, 2 H).

[1367]

(3)4-{[2-ethyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}benzoic acid

To a mixture of methyl 4-{[2-ethyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}benzoate (580 mg) synthesized

above, tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N aqueous sodium hydroxide solution (10.0 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (10.0 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (529 mg, 95%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.87 - 0.99 (m, 6 H), 1.32 - 1.56 (m, 3 H), 1.67 - 1.83 (m, 2 H), 2.46 (s, 3 H), 4.46 - 4.54 (m, 1 H), 4.82 - 4.91 (m, 1 H), 6.53 (d, J=8.7 Hz, 2 H), 7.22 - 7.30 (m, 1 H), 7.32 - 7.39 (m, 1 H), 7.65 (d, J=7.6 Hz, 1 H), 7.70 (d, J=7.6 Hz, 1 H), 7.81 (d, J=8.7 Hz, 2 H).

[1368]

(4) ethyl 3-{[(4-{[2-ethyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[2-ethyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}benzoic acid (250 mg) synthesized above, β-alanine ethyl ester hydrochloride (157 mg), 1-hydroxybenzotriazole monohydrate (156 mg), triethylamine (284 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (196 mg), and the mixture was stirred at room temperature for 2.5 days. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (330 mg, quantitative) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 - 0.97 (m, 6 H), 1.24 (t, J=7.1 Hz, 3 H), 1.33 - 1.55 (m, 3 H), 1.67 - 1.83 (m, 2 H), 2.46 (s, 3 H), 2.54 - 2.60 (m, 2 H), 3.60 - 3.68 (m, 2 H), 4.12 (q, J=7.1 Hz, 2 H), 4.35 (d, J=6.6 Hz, 1 H), 4.79 - 4.86

(m, 1 H), 6.50 - 6.61 (m, 3 H), 7.22 - 7.29 (m, 1 H), 7.31 - 7.37 (m, 1 H), 7.52 (d, J=8.5 Hz, 2 H), 7.61 - 7.66 (m, 1 H), 7.66 - 7.71 (m, 1 H).

[1369]

(5)3-{[(4-{[2-ethyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[2-ethyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}phenyl)carbonyl]amino}propanoate (330 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (272 mg, 91%) as a pale-yellow solid.

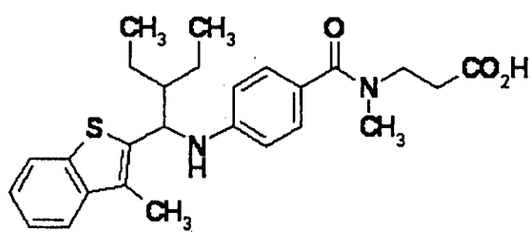
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 - 0.97 (m, 6 H), 1.32 - 1.56 (m, 3 H), 1.66 - 1.83 (m, 2 H), 2.45 (s, 3 H), 2.60 (t, J=5.5 Hz, 2 H), 3.57 - 3.66 (m, 2 H), 4.82 (d, J=6.0 Hz, 1 H), 6.47 - 6.58 (m, 3 H), 7.22 - 7.29 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.50 (d, J=8.7 Hz, 2 H), 7.64 (d, J=7.5 Hz, 1 H), 7.69 (d, J=7.9 Hz, 1 H).

[1370]

Example A135

3-{[(4-{[2-ethyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1371]




[1372]

(1) ethyl 3-{[(4-{[2-ethyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[2-ethyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}benzoic acid (250 mg) synthesized in Example A134(3), ethyl 3-(methylamino)propanoate (134 mg), 1-hydroxybenzotriazole monohydrate (156 mg), triethylamine (284 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (196 mg), and the mixture was stirred at room temperature 2.5 days. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine and saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (253 mg, 77%) as a colorless oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.87 - 0.97 (m, 6 H), 1.22 (t, J=7.1 Hz, 3 H), 1.32 - 1.54 (m, 3 H), 1.67 - 1.82 (m, 2 H), 2.45 (s, 3 H), 2.60 (t, J=7.0 Hz, 2 H), 3.00 (s, 3 H), 3.69 (t, J=7.0 Hz, 2 H), 4.10 (q, J=7.1 Hz, 2 H), 4.23 (d, J=6.3 Hz, 1 H), 4.76 - 4.83 (m, 1 H), 6.51 (d, J=8.8 Hz, 2 H), 7.19 (d, J=8.8 Hz, 2 H), 7.22 - 7.29 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.61 - 7.66 (m, 1 H), 7.68 - 7.72 (m, 1 H).

[1373]

(2)3-{[(4-{[2-ethyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[2-ethyl-1-(3-methyl-1-benzothiophen-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoate (253 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added

at 0°C. The resulting precipitate was collected by filtration to give the title object compound (225 mg, 95%) as a white solid.

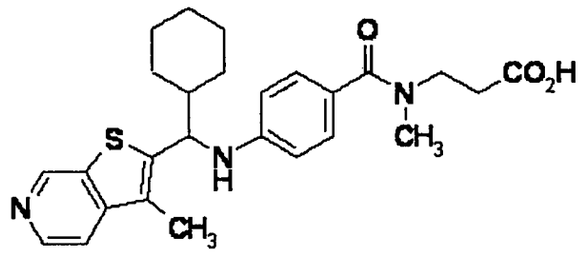
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.84 - 0.99 (m, 6 H), 1.30 - 1.56 (m, 3 H), 1.66 - 1.81 (m, 2 H), 2.45 (s, 3 H), 2.64 (t, J=6.4 Hz, 2 H), 3.01 (s, 3 H), 3.68 (t, J=6.4 Hz, 2 H), 4.80 (d, J=6.4 Hz, 1 H), 6.52 (d, J=8.7 Hz, 2 H), 7.21 (d, J=8.7 Hz, 2 H), 7.23 - 7.30 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.64 (d, J=7.9 Hz, 1 H), 7.71 (d, J=7.5 Hz, 1 H).

[1374]

Example A136

3-{[(4-{[cyclohexyl(3-methylthieno[2,3-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1375]



[1376]

(1) ethyl 3-methylthieno[2,3-c]pyridine-2-carboxylate

To a solution (120 mL) of 3-chloropyridine-4-carbonitrile (10.3 g) in tetrahydrofuran was added a 3.0M solution (49.8 mL) of methylmagnesium chloride in tetrahydrofuran under nitrogen atmosphere at 0°C, and the mixture was stirred at room temperature for 2 hr. Water (50 mL) was added to the reaction mixture, then 10% sulfuric acid (100 mL) was added to the reaction mixture, and the mixture was stirred overnight. Sodium carbonate was added to acidify the solution to pH=9, and the mixture was extracted with ethyl acetate. The extract was dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give a colorless oil (6.10 g). To a mixture

of the obtained oil (6.00 g), ethyl mercaptoacetate (11.6 mL) and anhydrous N,N-dimethylformamide (100 mL) was added sodium hydride (60%, oily, 4.0 g) at 5°C over 30 min, and the mixture was stirred at 5°C for 20 min then at room temperature overnight. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was poured into water. The precipitated solid was collected by filtration and recrystallized from petroleum ether/ethyl acetate to give the title object compound (5.12 g, 31%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.42 (t, J = 7.2 Hz, 3H), 2.76 (s, 3H), 4.41 (q, J = 7.2 Hz, 2H), 7.69 (dd, J = 5.7, 0.9 Hz, 1H), 8.57 (d, J = 5.7 Hz, 1H), 9.14 (d, J = 0.6 Hz, 1H).

[1377]

(2)3-methylthieno[2,3-c]pyridine-2-carbaldehyde

To a mixture of ethyl 3-methylthieno[2,3-c]pyridine-2-carboxylate (2.00 g) synthesized above, calcium chloride (2.01 g), ethanol (30 mL) and tetrahydrofuran (30 mL) was added sodium borohydride (1.37 g) at 0°C, and the mixture was stirred at room temperature for 3 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a pale-yellow solid. To a solution (40 mL) of the obtained solid in tetrahydrofuran was added active manganese dioxide (8.10 g), and the mixture was stirred at 50°C for 8 hr. Manganese dioxide was filtered off, and the filtrate was concentrated under reduced pressure to give the title object compound (1.39 g, 87%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.81 (s, 3 H), 7.75 (dd, J=5.5, 1.1 Hz, 1 H), 8.61 (d, J=5.5 Hz, 1 H), 9.20 (d, J=1.1 Hz, 1 H), 10.41 (s, 1 H).

[1378]

(3)cyclohexyl(3-methylthieno[2,3-c]pyridin-2-yl)methanone

602

To a solution (30 mL) of 3-methylthieno[2,3-c]pyridine-2-carbaldehyde (1.39 g) synthesized above in tetrahydrofuran was added a 1.0M solution (15.7 mL) of cyclohexylmagnesium bromide in tetrahydrofuran at 0°C, and the mixture was stirred for 1.5 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, tetrahydrofuran was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give a pale-yellow solid. To a mixture of the obtained solid, 4-methylmorpholine N-oxide (680 mg) and acetonitrile (20 mL) was added tetrapropylammonium perruthenate (113 mg), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 40% ethyl acetate/hexane) to give the title object compound (628 mg, 31%) as a colorless oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.22 - 1.62 (m, 5 H), 1.70 - 1.81 (m, 1 H), 1.82 - 1.94 (m, 2 H), 1.95 - 2.06 (m, 2 H), 2.73 (s, 3 H), 2.97 - 3.09 (m, 1 H), 7.71 (dd, J=5.5, 1.1 Hz, 1 H), 8.58 (d, J=5.5 Hz, 1 H), 9.16 (d, J=1.1 Hz, 1 H).

[1379]

(4)4-{[cyclohexyl(3-methylfuro[2,3-c]pyridin-2-yl)methyl]amino}benzoic acid

To a mixture of cyclohexyl(3-methylthieno[2,3-c]pyridin-2-yl)methanone (628 mg) synthesized above, methyl 4-aminobenzoate (402 mg), triethylamine (2.70 mL) and methylene chloride (10 mL) was added titanium (IV) chloride (318 μL), and the mixture was stirred under argon atmosphere overnight at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown

oil. To a solution (30 mL) of the obtained oil in tetrahydrofuran were added acetic acid (277 µL) and sodium cyanoborohydride (304 mg), and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, the organic solvent was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give an orange solid. To a mixture of the obtained solid, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (5.00 mL), and the mixture was stirred with heating under reflux for 4 hr. 1N Hydrochloric acid (5.00 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (40 - 100% ethyl acetate/hexane) to give the title object compound (202 mg, 22%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.07 - 1.34 (m, 5 H), 1.40 - 1.93 (m, 5 H), 2.01 - 2.16 (m, 1 H), 2.50 (s, 3 H), 4.58 - 4.69 (m, 2 H), 6.51 (d, J=8.8 Hz, 2 H), 7.52 (dd, J=5.6, 0.9 Hz, 1 H), 7.82 (d, J=8.8 Hz, 2 H), 8.49 (d, J=5.6 Hz, 1 H), 8.95 (d, J=0.9 Hz, 1 H).

[1380]

(5) ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[2,3-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[cyclohexyl(3-methylfuro[2,3-c]pyridin-2-yl)methyl]amino}benzoic acid (202 mg) synthesized above, ethyl 3-(methylamino)propanoate (104 mg), 1-hydroxybenzotriazole monohydrate (122 mg), triethylamine (222 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (152 mg), and

the mixture was stirred at room temperature for 1 day. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 100% ethyl acetate/hexane, then 0 - 10% methanol/acetic acid) to give the title object compound (151 mg, 58%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.06 - 1.36 (m, 8 H), 1.53 - 1.88 (m, 5 H), 2.03 - 2.16 (m, 1 H), 2.48 (s, 3 H), 2.60 (t, J=7.0 Hz, 2 H), 2.99 (s, 3 H), 3.69 (t, J=7.0 Hz, 2 H), 4.10 (q, J=7.1 Hz, 2 H), 4.35 (d, J=5.7 Hz, 1 H), 4.58 (dd, J=7.3, 5.7 Hz, 1 H), 6.49 (d, J=8.7 Hz, 2 H), 7.19 (d, J=8.7 Hz, 2 H), 7.51 (dd, J=5.7, 1.1 Hz, 1 H), 8.48 (d, J=5.7 Hz, 1 H), 8.95 (d, J=1.1 Hz, 1 H).

[1381]

(6)3-{[(4-{[cyclohexyl(3-methylthieno[2,3-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[2,3-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (151 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 5 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (80.2 mg, 56%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 - 1.34 (m, 5 H), 1.50 - 1.62 (m, 1 H), 1.63 - 1.88 (m, 4 H), 2.02 - 2.14 (m, 1 H), 2.48 (s, 3 H), 2.53 - 2.68 (m, 2 H), 3.00 (s, 3 H), 3.58 - 3.74 (m, 2 H), 4.57 (d, J=7.5 Hz, 1 H), 6.47 (d, J=8.5 Hz, 2 H), 7.19 (d,

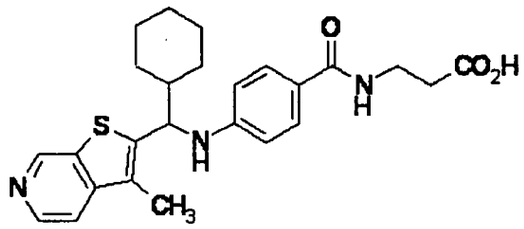
J=8.5 Hz, 2 H), 7.55 (d, J=5.7 Hz, 1 H), 8.43 (d, J=5.7 Hz, 1 H), 8.94 (s, 1 H).

[1382]

Example A137

3-{[(4-{[cyclohexyl(3-methylthieno[2,3-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1383]



[1384]

(1) ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[2,3-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[cyclohexyl(3-methylfuro[2,3-c]pyridin-2-yl)methyl]amino}benzoic acid (201 mg) synthesized in Example A136(4), β-alanine ethyl ester hydrochloride (122 mg), 1-hydroxybenzotriazole monohydrate (121 mg), triethylamine (220 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (152 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60 - 100% ethyl acetate/hexane) to give the title object compound (209 mg, 83%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.06 - 1.37 (m, 8 H), 1.53 - 1.89 (m, 5 H), 2.05 - 2.16 (m, 1 H), 2.48 (s, 3 H), 2.56 (t, J=5.8 Hz, 2 H), 3.59 - 3.68 (m, 2 H), 4.12 (q, J=7.1 Hz, 2 H), 4.50

(d, J=5.8 Hz, 1 H), 4.58 - 4.64 (m, 1 H), 6.50 (d, J=8.8 Hz, 2 H), 6.61 (t, J=5.9 Hz, 1 H), 7.51 (dd, J=5.5, 1.1 Hz, 1 H), 7.52 (d, J=8.8 Hz, 2 H), 8.47 (d, J=5.5 Hz, 1 H), 8.93 (d, J=1.1 Hz, 1 H).

[1385]

(2)3-{[(4-{[cyclohexyl(3-methylthieno[2,3-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[2,3-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate (209 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (169 mg, 86%) as a white solid.

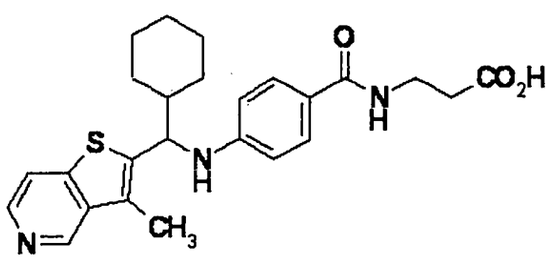
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 - 1.36 (m, 5 H), 1.49 - 1.89 (m, 5 H), 2.02 - 2.14 (m, 1 H), 2.48 (s, 3 H), 2.59 (t, J=5.7 Hz, 2 H), 3.51 - 3.77 (m, 2 H), 4.59 (d, J=7.2 Hz, 1 H), 6.47 (d, J=8.7 Hz, 2 H), 6.85 (t, J=5.8 Hz, 1 H), 7.48 - 7.60 (m, 3 H), 8.42 (d, J=5.7 Hz, 1 H), 8.88 (s, 1 H).

[1386]

Example A138

3-{[(4-{[cyclohexyl(3-methylthieno[3,2-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1387]



607

[1388]

(1) ethyl 3-methylthieno[3,2-c]pyridine-2-carboxylate

Thionyl chloride (100 mL) was added to 4-chloronicotinic acid (22.4 g), and the mixture was stirred with heating under reflux for 4 hr, and concentrated under reduced pressure. To a solution (300 mL) of the residue in methylene chloride were added N,O-dimethylhydroxylamine hydrochloride (13.8 g) and triethylamine (60 mL), and the mixture was stirred at room temperature for 5 hr. Water was added to the reaction mixture, and the reaction mixture was extracted with methylene chloride. The extract was dried over sodium sulfate, and concentrated under reduced pressure. To a solution (300 mL) of the residue in tetrahydrofuran was added a 3.0 M solution (54 mL) of methylmagnesium chloride in ether at -78°C and the mixture was stirred under nitrogen atmosphere at room temperature for 10 hr. The reaction mixture was acidified with aqueous sodium carbonate solution to pH=9, and extracted with ethyl acetate. The extract was dried over sodium sulfate, and concentrated under reduced pressure to give a colorless oil. To a mixture of the obtained oil, ethyl mercaptoacetate (21 mL) and anhydrous N,N-dimethylformamide (200 mL) was added sodium hydride (60%, oily, 7.34 g) at 5°C over 30 min, and the mixture was stirred at 5°C for 20 min then at room temperature for 18 hr. Water was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was dried over sodium sulfate, and concentrated under reduced pressure. The obtained solid was recrystallized from petroleum ether/ethyl acetate to give the title object compound (5.45 g, 17%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.43 (t, J = 7.2 Hz, 3H), 2.85 (s, 3H), 4.42 (q, J = 7.2 Hz, 2H), 7.74 (dd, J = 5.7, 0.9 Hz, 1H), 8.55 (d, J = 6.0 Hz, 1H), 9.14 (d, J = 1.2 Hz, 1H).

(2)3-methylthieno[3,2-c]pyridine-2-carbaldehyde

To a mixture of ethyl 3-methylthieno[3,2-c]pyridine-2-carboxylate (3.40 g) synthesized above, calcium chloride (3.42

g), ethanol (30 mL) and tetrahydrofuran (30 mL) was added sodium borohydride (2.33 g) at 0°C, and the mixture was stirred at room temperature for 3 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a pale-yellow oil. To a solution (60 mL) of the obtained oil in tetrahydrofuran was added active manganese dioxide (14.4 g) and the mixture was stirred at 50°C overnight. Manganese dioxide was filtered off, and the filtrate was concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title object compound (1.54 g, 56%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.89 (s, 3 H), 7.79 (dd, J=5.5, 0.8 Hz, 1 H), 8.58 (d, J=5.5 Hz, 1 H), 9.21 (d, J=0.8 Hz, 1 H), 10.35 (s, 1 H).

[1389]

(3)cyclohexyl(3-methylthieno[3,2-c]pyridin-2-yl)methanone

To a solution (40 mL) of 3-methylthieno[3,2-c]pyridine-2-carbaldehyde (1.87 g) synthesized above in tetrahydrofuran was added a 1.0M solution (21.2 mL) of cyclohexylmagnesium bromide in tetrahydrofuran at 0°C, and the mixture was stirred for 1 hr. A 1.0M solution (10.0 mL) of cyclohexylmagnesium bromide in tetrahydrofuran was additionally added, and the mixture was further stirred at 0°C for 1 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 90% ethyl acetate/hexane) to give a pale-yellow solid. To a mixture of the obtained solid, 4-methylmorpholine N-oxide (1.24 mg) and acetonitrile (30 mL) was added tetrapropylammonium perruthenate (164 mg), and the mixture was stirred at room

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temperature for 4 hr, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 - 50% ethyl acetate/hexane) to give the title object compound (864 mg, 31%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.19 - 1.61 (m, 5 H), 1.69 - 1.80 (m, 1 H), 1.81 - 1.92 (m, 2 H), 1.93 - 2.04 (m, 2 H), 2.82 (s, 3 H), 2.93 - 3.05 (m, 1 H), 7.75 (dd, J=5.7, 1.0 Hz, 1 H), 8.55 (d, J=5.7 Hz, 1 H), 9.17 (d, J=1.0 Hz, 1 H).

[1390]

(4)4-{[cyclohexyl(3-methylfuro[3,2-c]pyridin-2-yl)methyl]amino}benzoic acid

To a mixture of cyclohexyl(3-methylthieno[3,2-c]pyridin-2-yl)methanone (864 mg) synthesized above, methyl 4-aminobenzoate (553 mg), triethylamine (3.71 mL) and methylene chloride (20 mL) was added titanium (IV) chloride (439 µL) at 0°C, and the mixture was stirred under argon atmosphere overnight at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (20 mL) of the obtained oil in tetrahydrofuran were added acetic acid (268 µL) and sodium cyanoborohydride (419 mg), and the mixture was stirred at room temperature stirred for 1.5 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give a pale-brown solid. To a mixture of the obtained solid, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (5.00 mL), and the mixture was stirred overnight with heating under reflux. Tetrahydrofuran (5 mL), ethanol (5 mL) and 1N aqueous

sodium hydroxide solution (5.00 mL) were additionally added, and the mixture was stirred with heating under reflux for 2.5 hr, and ethylenediamine (1.00 mL) was added. The mixture was stirred with heating under reflux for 4 hr, and concentrated under reduced pressure. The residue was acidified with 1N hydrochloric acid to pH=4, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50 - 100% ethyl acetate/hexane) to give the title object compound (432 mg, 34%) as a pale-yellow solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 - 1.37 (m, 5 H), 1.53 - 1.90 (m, 5 H), 2.03 - 2.15 (m, 1 H), 2.56 (s, 3 H), 4.55 - 4.66 (m, 2 H), 6.51 (d, J=8.7 Hz, 2 H), 7.63 (dd, J=5.5, 1.1 Hz, 1 H), 7.84 (d, J=8.7 Hz, 2 H), 8.39 (d, J=5.5 Hz, 1 H), 8.97 (d, J=1.1 Hz, 1 H).

[1391]

(5) ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[3,2-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[cyclohexyl(3-methylfuro[3,2-c]pyridin-2-yl)methyl]amino}benzoic acid (211 mg) synthesized above, β-alanine ethyl ester hydrochloride (128 mg), 1-hydroxybenzotriazole monohydrate (128 mg), triethylamine (233 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (160 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60 - 100% ethyl acetate/hexane) to give the title object compound (214 mg, 80%) as a white solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.05 - 1.37 (m, 8 H), 1.53 - 1.91

(m, 5 H), 2.04 - 2.16 (m, 1 H), 2.50 - 2.63 (m, 5 H), 3.58 - 3.70 (m, 2 H), 4.12 (q, J=7.1 Hz, 2 H), 4.42 (d, J=5.8 Hz, 1 H), 4.52 - 4.62 (m, 1 H), 6.51 (d, J=8.7 Hz, 2 H), 6.59 (t, J=5.8 Hz, 1 H), 7.52 (d, J=8.7 Hz, 2 H), 7.60 (d, J=5.5 Hz, 1 H), 8.37 (d, J=5.5 Hz, 1 H), 8.93 (s, 1 H).

[1392]

(6)3-{[(4-{[cyclohexyl(3-methylthieno[3,2-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[3,2-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate (186 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (186 mg, 93%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.05 - 1.36 (m, 5 H), 1.55 - 1.64 (m, 1 H), 1.65 - 1.90 (m, 4 H), 2.03 - 2.15 (m, 1 H), 2.56 (s, 3 H), 2.61 (t, J=5.1 Hz, 2 H), 3.52 - 3.67 (m, 1 H), 3.73 - 3.89 (m, 1 H), 4.56 (d, J=7.2 Hz, 1 H), 6.48 (d, J=8.7 Hz, 2 H), 6.89 - 6.99 (m, 1 H), 7.58 (d, J=8.7 Hz, 2 H), 7.69 (d, J=5.7 Hz, 1 H), 8.31 (d, J=5.7 Hz, 1 H), 8.96 (s, 1 H).

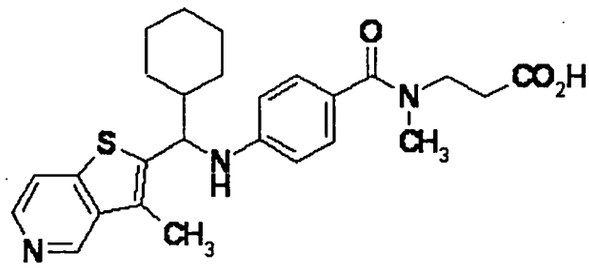
[1393]

Example A139

3-{[(4-{[cyclohexyl(3-methylthieno[3,2-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1394]

612



[1395]

(1) ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[3,2-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[cyclohexyl(3-methylfuro[3,2-c]pyridin-2-yl)methyl]amino}benzoic acid (209 mg) synthesized in Example A138(4), ethyl 3-(methylamino)propanoate (108 mg), 1-hydroxybenzotriazole monohydrate (126 mg), triethylamine (229 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (158 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60 - 100% ethyl acetate/hexane, then 0 - 10% methanol/ethyl acetate) to give the title object compound (180 mg, 66%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 - 1.38 (m, 8 H), 1.52 - 1.94 (m, 5 H), 2.02 - 2.16 (m, 1 H), 2.55 (s, 3 H), 2.60 (t, J=6.9 Hz, 2 H), 2.99 (s, 3 H), 3.69 (t, J=6.9 Hz, 2 H), 4.10 (q, J=6.8 Hz, 2 H), 4.27 - 4.39 (m, 1 H), 4.49 - 4.59 (m, 1 H), 6.49 (d, J=8.5 Hz, 2 H), 7.19 (d, J=8.5 Hz, 2 H), 7.62 (d, J=5.5 Hz, 1 H), 8.38 (d, J=5.5 Hz, 1 H), 8.93 (s, 1 H).

[1396]

(2)3-{[(4-{[cyclohexyl(3-methylthieno[3,2-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[3,2-c]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (180 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) 1N aqueous sodium hydroxide solution (1.00 mL) was added, and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (1.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (136 mg, 80%) as a white solid.

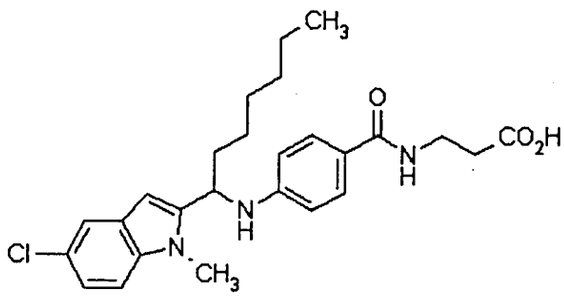
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 - 1.32 (m, 5 H), 1.52 - 1.63 (m, 1 H), 1.63 - 1.89 (m, 4 H), 2.03 - 2.15 (m, 1 H), 2.53 (s, 3 H), 2.58 - 2.74 (m, 2 H), 3.03 (s, 3 H), 3.62 - 3.79 (m, 2 H), 4.54 (d, J=7.5 Hz, 1 H), 6.48 (d, J=8.7 Hz, 2 H), 7.22 (d, J=8.7 Hz, 2 H), 7.67 (d, J=5.5 Hz, 1 H), 8.34 (d, J=5.5 Hz, 1 H), 8.93 (s, 1 H).

[1397]

Example A140

3-{[(4-{[1-(5-chloro-1-methyl-1H-indol-2-yl)heptyl]amino}phenyl)carbonyl]amino}propanoic acid

[1398]



[1399]

(1)1-(5-chloro-1-methyl-1H-indol-2-yl)heptan-1-one

To a solution (10 mL) of 1-(5-chloro-1H-indol-2-yl)heptan-1-one (1.00 g) synthesized in Example A106(2) in N,N-dimethylformamide was added sodium hydride (60%, oily, 182 mg) at 0°C and the mixture was stirred under argon atmosphere

for 30 min. After stirring, methyl iodide (354 μL) was added. The reaction mixture was stirred at room temperature overnight, saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with hexane to give the title object compound (367 mg, 35%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 - 0.94 (m, 3 H), 1.24 - 1.46 (m, 6 H), 1.68 - 1.81 (m, 2 H), 2.90 - 2.98 (m, 2 H), 4.05 (s, 3 H), 7.19 (s, 1 H), 7.28 - 7.31 (m, 2 H), 7.63 - 7.66 (m, 1 H).

[1400]

(2) methyl 4-{[1-(5-chloro-1-methyl-1H-indol-2-yl)heptyl]amino}benzoate

To a mixture of 1-(5-chloro-1-methyl-1H-indol-2-yl)heptan-1-one (1.05 g) synthesized above, methyl 4-aminobenzoate (629 mg), triethylamine (4.21 mL) and methylene chloride (10 mL) was added a 1.0M solution (4.54 mL) of titanium (IV) chloride in methylene chloride at 0°C, and the mixture was stirred overnight at room temperature under argon atmosphere. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown solid. To a solution (10 mL) of the obtained solid in tetrahydrofuran were added acetic acid (1.08 mL) and sodium cyanoborohydride (475 mg), and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 30% ethyl

acetate/hexane) to give the title object compound (1.15 g, 74%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.83 - 0.91 (m, 3 H), 1.21 - 1.53 (m, 8 H), 1.88 - 2.08 (m, 2 H), 3.68 (s, 3 H), 3.83 (s, 3 H), 4.25 (d, J=7.1 Hz, 1 H), 4.60 - 4.70 (m, 1 H), 6.37 (s, 1 H), 6.55 (d, J=8.8 Hz, 2 H), 7.13 (dd, J=8.7, 1.9 Hz, 1 H), 7.19 (d, J=8.7 Hz, 1 H), 7.49 (d, J=1.9 Hz, 1 H), 7.83 (d, J=8.8 Hz, 2 H).

[1401]

(3)4-{[1-(5-chloro-1-methyl-1H-indol-2-yl)heptyl]amino}benzoic acid

To a mixture of methyl 4-{[1-(5-chloro-1-methyl-1H-indol-2-yl)heptyl]amino}benzoate (1.15 g) synthesized above, tetrahydrofuran (15 mL) and ethanol (15 mL) was added 1N aqueous sodium hydroxide solution (15 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (30 mL), and 1N hydrochloric acid (15 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (1.09 g, 98%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 (t, J=6.5 Hz, 3 H), 1.11 - 1.51 (m, 8 H), 1.79 - 2.04 (m, 2 H), 3.58 (s, 3 H), 4.49 - 4.63 (m, 1 H), 6.31 (s, 1 H), 6.42 (d, J=8.3 Hz, 2 H), 7.05 - 7.17 (m, 2 H), 7.46 (s, 1 H), 7.80 (d, J=8.3 Hz, 2 H).

[1402]

(4) ethyl 3-{[(4-{[1-(5-chloro-1-methyl-1H-indol-2-yl)heptyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[1-(5-chloro-1-methyl-1H-indol-2-yl)heptyl]amino}benzoic acid (300 mg) synthesized above, β-alanine ethyl ester hydrochloride (174 mg), 1-hydroxybenzotriazole monohydrate (173 mg), triethylamine (158 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (217 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to

quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (349 mg, 93%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.88 (t, J=6.9 Hz, 3 H), 1.18 - 1.55 (m, 11 H), 1.87 - 2.10 (m, 2 H), 2.60 (t, J=5.8 Hz, 2 H), 3.61 - 3.76 (m, 5 H), 4.06 - 4.23 (m, 3 H), 4.57 - 4.69 (m, 1 H), 6.37 (s, 1 H), 6.57 (d, J=8.5 Hz, 2 H), 6.64 (t, J=5.8 Hz, 1 H), 7.11 - 7.16 (m, 1 H), 7.17 - 7.23 (m, 1 H), 7.50 (d, J=1.6 Hz, 1 H), 7.59 (d, J=8.5 Hz, 2 H).

[1403]

(5)3-{[(4-{[1-(5-chloro-1-methyl-1H-indol-2-yl)heptyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[1-(5-chloro-1-methyl-1H-indol-2-yl)heptyl]amino}phenyl)carbonyl]amino}propanoate (349 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 3 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (302 mg, 92%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 (t, J=6.4 Hz, 3 H), 1.17 - 1.55 (m, 8 H), 1.84 - 2.05 (m, 2 H), 2.62 (t, J=5.7 Hz, 2 H), 3.58 - 3.72 (m, 5 H), 4.60 (t, J=6.8 Hz, 1 H), 6.33 (s, 1 H), 6.52 (d, J=8.7 Hz, 2 H), 6.69 (t, J=5.8 Hz, 1 H), 7.12 (dd, J=9.0, 2.1 Hz, 1 H), 7.17 (d, J=9.0 Hz, 1 H), 7.47 (d, J=2.1 Hz, 1 H), 7.55 (d, J=8.7 Hz, 2 H).

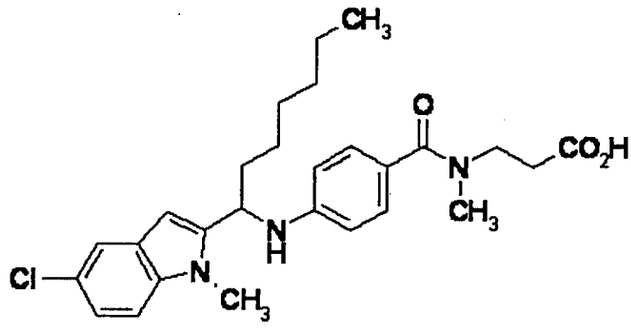
[1404]

Example A141

3-{[(4-{[1-(5-chloro-1-methyl-1H-indol-2-

yl)heptyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1405]



[1406]

(1) ethyl 3-{[(4-{[1-(5-chloro-1-methyl-1H-indol-2-yl)heptyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[1-(5-chloro-1-methyl-1H-indol-2-yl)heptyl]amino}benzoic acid (300 mg) synthesized in Example A140(3), ethyl 3-(methylamino)propanoate (148 mg), 1-hydroxybenzotriazole monohydrate (173 mg), triethylamine (158 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (217 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (235 mg, 61%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.87 (t, J=6.6 Hz, 3 H), 1.17 - 1.53 (m, 11 H), 1.89 - 2.06 (m, 2 H), 2.63 (t, J=6.7 Hz, 2 H), 3.04 (s, 3 H), 3.65 - 3.79 (m, 5 H), 4.02 (d, J=7.1 Hz, 1 H), 4.12 (q, J=7.1 Hz, 2 H), 4.54 - 4.65 (m, 1 H), 6.37 (s, 1 H), 6.55 (d, J=8.4 Hz, 2 H), 7.13 (dd, J=8.8, 1.8 Hz, 1 H), 7.20 (d, J=8.8 Hz, 1 H), 7.25 (d, J=8.4 Hz, 2 H), 7.50 (d, J=1.8 Hz, 1 H).

[1407]

(2)3-{[(4-{[1-(5-chloro-1-methyl-1H-indol-2-yl)heptyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[1-(5-chloro-1-methyl-1H-indol-2-yl)heptyl]amino}phenyl)carbonyl](methyl)amino}propanoate (235 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (211 mg, 95%) as a pale-yellow solid.

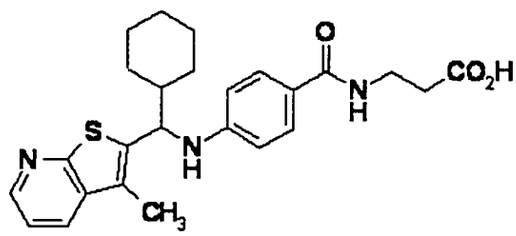
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.87 (t, J=6.8 Hz, 3 H), 1.16 - 1.54 (m, 8 H), 1.84 - 2.05 (m, 2 H), 2.63 (t, J=5.8 Hz, 2 H), 3.02 (s, 3 H), 3.62 - 3.76 (m, 5 H), 4.59 (t, J=6.8 Hz, 1 H), 6.35 (s, 1 H), 6.53 (d, J=8.5 Hz, 2 H), 7.12 (dd, J=8.7, 1.9 Hz, 1 H), 7.19 (d, J=8.7 Hz, 1 H), 7.24 (d, J=8.5 Hz, 2 H), 7.49 (d, J=1.9 Hz, 1 H).

[1408]

Example A142

3-{[(4-{[cyclohexyl(3-methylthieno[2,3-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1409]




[1410]

(1) ethyl 3-methylthieno[2,3-b]pyridine-2-carboxylate

To a solution (300 mL) of 2-chloropyridine-3-carbonitrile (15.0 g) in tetrahydrofuran was added a 3.0M solution (72.5

mL) of methylmagnesium chloride in tetrahydrofuran at -78°C, and the mixture was stirred at room temperature for 10 hr under nitrogen atmosphere. To the reaction mixture was added water (50 mL), and then added 10% sulfuric acid (100 mL), and the mixture was stirred overnight. Sodium carbonate was added to acidify the reaction mixture to pH=9, and the mixture was extracted with ethyl acetate. The extract was dried with sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give a colorless oil (7.68 g). To a mixture of the obtained oil (7.00 g), ethyl mercaptoacetate (13 mL) and anhydrous N,N-dimethylformamide (200 mL) was added sodium hydride (60%, oily, 4.68 g) at 5°C over 30 min, and the mixture was stirred at 5°C for 20 min then at room temperature for 18 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the mixture was poured into water. The precipitated solid was collected by filtration and recrystallized from petroleum ether/ethyl acetate to give the title object compound (6.14 g, 29%) as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$) δ ppm 1.45 (t, J = 7.2 Hz, 3H), 2.78 (s, 3H), 4.43 (q, J = 7.2 Hz, 2H), 7.38-7.40 (m, 1H), 8.11-8.13 (m, 1H), 8.70-8.72 (m, 1H).

[1411]

(2)3-methylthieno[2,3-b]pyridine-2-carbaldehyde

To a mixture of ethyl 3-methylthieno[2,3-b]pyridine-2-carboxylate (3.00 g) synthesized above, calcium chloride (3.02 g), ethanol (50 mL) and tetrahydrofuran (50 mL) was added sodium borohydride (2.06 g) at 0°C, and the mixture was stirred at room temperature for 4 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a white solid. To a solution (50 mL) of the obtained solid in tetrahydrofuran was added active manganese dioxide (12.5 g), and the mixture

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was stirred at 50°C overnight. Manganese dioxide was filtered off, and the filtrate was concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title object compound (2.07 g, 86%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.79 (s, 3 H), 7.39 (dd, J=8.2, 4.5 Hz, 1 H), 8.16 (dd, J=8.2, 1.6 Hz, 1 H), 8.72 (dd, J=4.5, 1.6 Hz, 1 H), 10.36 (s, 1 H).

[1412]

(3)cyclohexyl(3-methylthieno[2,3-b]pyridin-2-yl)methanone

To a solution (60 mL) of 3-methylthieno[2,3-b]pyridine-2-carbaldehyde (2.07 g) synthesized above in tetrahydrofuran was added a 1.0M solution (17.6 mL) of cyclohexylmagnesium bromide in tetrahydrofuran at 0°C, and the mixture was stirred for 1 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 - 50% ethyl acetate/hexane) to give a yellow solid. To a mixture of the obtained solid, 4-methylmorpholine N-oxide (1.81 g) and acetonitrile (40 mL) was added tetrapropylammonium perruthenate (238 mg), and the mixture was stirred at room temperature for 3 hr, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 30% ethyl acetate/hexane) to give the title object compound (1.50 g, 85%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.18 - 1.62 (m, 5 H), 1.69 - 1.80 (m, 1 H), 1.81 - 1.91 (m, 2 H), 1.95 - 2.06 (m, 2 H), 2.73 (s, 3 H), 2.95 - 3.07 (m, 1 H), 7.37 (m, J=8.2, 4.4 Hz, 1 H), 8.13 (dd, J=8.2, 1.6 Hz, 1 H), 8.70 (dd, J=4.4, 1.6 Hz, 1 H).

[1413]

(4) methyl 4-{[cyclohexyl(3-methylfuro[2,3-b]pyridin-2-yl)methyl]amino}benzoate

To a mixture of cyclohexyl(3-methylthieno[2,3-b]pyridin-

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2-yl)methanone (1.00 g) synthesized above, methyl 4-aminobenzoate (642 mg), triethylamine (4.31 mL) and methylene chloride (20 mL) was added titanium (IV) chloride (508 μL) at 0°C, and the mixture was stirred at room temperature for 1.5 days under argon atmosphere. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown solid. To a solution (20 mL) of the obtained solid in tetrahydrofuran were added acetic acid (442 μL) and sodium cyanoborohydride (485 mg), and the mixture was stirred at room temperature for 1.5 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (975 mg, 64%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 1.35 (m, 5 H), 1.48 - 1.96 (m, 5 H), 2.02 - 2.19 (m, 1 H), 2.55 (s, 3 H), 3.81 (s, 3 H), 4.54 - 4.70 (m, 2 H), 6.51 (d, J=8.8 Hz, 2 H), 7.59 (dd, J=7.6, 5.7 Hz, 1 H), 7.78 (d, J=8.8 Hz, 2 H), 8.22 (d, J=7.6 Hz, 1 H), 8.63 (d, J=5.7 Hz, 1 H).

[1414]

(5)4-{[cyclohexyl(3-methylfuro[2,3-b]pyridin-2-yl)methyl]amino}benzoic acid

To a mixture of methyl 4-{[cyclohexyl(3-methylfuro[2,3-b]pyridin-2-yl)methyl]amino}benzoate (975 mg) synthesized above, tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N aqueous sodium hydroxide solution (10 mL), and the mixture was stirred overnight with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (20 mL), 1N hydrochloric acid (10 mL) was added, and

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the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (701 mg, 75%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.01 - 1.39 (m, 5 H), 1.53 - 1.92 (m, 5 H), 2.07 - 2.20 (m, 1 H), 2.46 (s, 3 H), 4.60 (d, J=8.0 Hz, 1 H), 6.53 (d, J=8.5 Hz, 2 H), 7.21 - 7.31 (m, 1 H), 7.82 (d, J=8.5 Hz, 2 H), 7.87 (dd, J=8.1, 1.3 Hz, 1 H), 8.47 (dd, J=4.4, 1.3 Hz, 1 H).

[1415]

(6) ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[2,3-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[cyclohexyl(3-methylfuro[2,3-b]pyridin-2-yl)methyl]amino}benzoic acid (300 mg) synthesized above, β-alanine ethyl ester hydrochloride (181 mg), 1-hydroxybenzotriazole monohydrate (181 mg), triethylamine (329 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (226 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 100% ethyl acetate/hexane) to give the title object compound (335 mg, 89%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.38 (m, 8 H), 1.54 - 1.90 (m, 5 H), 2.08 - 2.21 (m, 1 H), 2.45 (s, 3 H), 2.56 (t, J=5.9 Hz, 2 H), 3.59 - 3.69 (m, 2 H), 4.12 (q, J=7.1 Hz, 2 H), 4.40 (d, J=6.3 Hz, 1 H), 4.53 - 4.61 (m, 1 H), 6.48 - 6.64 (m, 3 H), 7.21 - 7.30 (m, 1 H), 7.52 (d, J=8.5 Hz, 2 H), 7.86 (dd, J=8.1, 1.5 Hz, 1 H), 8.45 (dd, J=4.5, 1.5 Hz, 1 H).

[1416]

(7)3-{[(4-{[cyclohexyl(3-methylthieno[2,3-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[2,3-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate (335 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (281 mg, 89%) as a white solid.

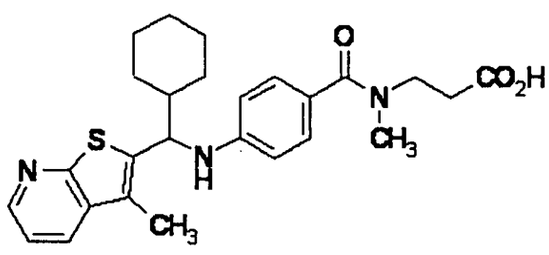
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 1.34 (m, 5 H), 1.51 - 1.87 (m, 5 H), 2.06 - 2.19 (m, 1 H), 2.44 (s, 3 H), 2.52 - 2.64 (m, 2 H), 3.53 - 3.68 (m, 2 H), 4.55 (d, J=8.0 Hz, 1 H), 6.49 (d, J=8.7 Hz, 2 H), 6.71 (t, J=5.3 Hz, 1 H), 7.23 - 7.31 (m, 1 H), 7.49 (d, J=8.7 Hz, 2 H), 7.88 (dd, J=8.0, 1.1 Hz, 1 H), 8.45 (dd, J=4.5, 1.1 Hz, 1 H).

[1417]

Example A143

3-{[(4-{[cyclohexyl(3-methylthieno[2,3-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1418]




[1419]

(1) ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[2,3-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

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To a mixture of 4-{[cyclohexyl(3-methylfuro[2,3-b]pyridin-2-yl)methyl]amino}benzoic acid (300 mg) synthesized in Example A142(5), ethyl 3-(methylamino)propanoate (155 mg), 1-hydroxybenzotriazole monohydrate (181 mg), triethylamine (329 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (226 mg), and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (40 - 100% ethyl acetate/hexane) to give the title object compound (333 mg, 85%) as a pale-yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 1.37 (m, 8 H), 1.52 - 1.89 (m, 5 H), 2.07 - 2.21 (m, 1 H), 2.45 (s, 3 H), 2.60 (t, J=6.8 Hz, 2 H), 2.99 (s, 3 H), 3.69 (t, J=6.8 Hz, 2 H), 4.02 - 4.17 (m, 2 H), 4.32 (d, J=5.8 Hz, 1 H), 4.49 - 4.58 (m, 1 H), 6.52 (d, J=8.5 Hz, 2 H), 7.19 (d, J=8.5 Hz, 2 H), 7.22 - 7.31 (m, 1 H), 7.86 (dd, J=8.0, 1.1 Hz, 1 H), 8.43 - 8.50 (m, 1 H).

[1420]

(2)3-{[(4-{[cyclohexyl(3-methylthieno[2,3-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[2,3-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (333 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 4 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (275 mg, 88%) as a white solid.

625

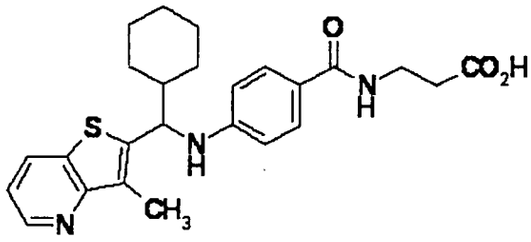
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.02 - 1.35 (m, 5 H), 1.54 - 1.88 (m, 5 H), 2.07 - 2.19 (m, 1 H), 2.45 (s, 3 H), 2.58 - 2.70 (m, 2 H), 3.01 (s, 3 H), 3.68 (t, J=6.6 Hz, 2 H), 4.54 (d, J=7.6 Hz, 1 H), 6.51 (d, J=8.7 Hz, 2 H), 7.20 (d, J=8.7 Hz, 2 H), 7.27 (dd, J=8.1, 4.7 Hz, 1 H), 7.88 (dd, J=8.1, 1.6 Hz, 1 H), 8.47 (dd, J=4.7, 1.6 Hz, 1 H).

[1421]

Example A144

3-{[(4-{[cyclohexyl(3-methylthieno[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1422]



[1423]

(1) ethyl 3-methylthieno[3,2-b]pyridine-2-carboxylate

To a solution (100 mL) of 3-chloropyridine-2-carbonitrile (10.0 g) in tetrahydrofuran was added a 3.0M solution (48.0 mL) of methylmagnesium bromide in diethyl ether, and the mixture was stirred at room temperature for 3 hr. To the reaction mixture was added 2N hydrochloric acid (300 mL), tetrahydrofuran was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give a pale-yellow oil. To a mixture of the obtained oil, ethyl mercaptoacetate (4.23 mL) and N,N-dimethylformamide (60 mL) was added and potassium carbonate (16.0 g), and the mixture was stirred overnight at 50°C. Water was added to quench the reaction, and the precipitated solid

was collected by filtration to give the title object compound (6.75 g, 79%) as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$) δ ppm 1.44 (t, J=7.2 Hz, 3 H), 2.87 (s, 3 H), 4.44 (q, J=7.2 Hz, 2 H), 7.37 (dd, J=8.3, 4.4 Hz, 1 H), 8.17 (dd, J=8.3, 1.5 Hz, 1 H), 8.78 (dd, J=4.4, 1.5 Hz, 1 H).

[1424]

(2)3-methylthieno[3,2-b]pyridine-2-carbaldehyde

To a mixture of ethyl 3-methylthieno[3,2-b]pyridine-2-carboxylate (3.00 g) synthesized above, calcium chloride (3.02 g), ethanol (30 mL) and tetrahydrofuran (30 mL) was added sodium borohydride (2.06 g) at 0°C, and the mixture was stirred at room temperature for 5 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a white solid. To a solution (50 mL) of the obtained solid in tetrahydrofuran was added active manganese dioxide (12.2 g), and the mixture was stirred at 50°C overnight. Manganese dioxide was filtered off, and the filtrate was concentrated under reduced pressure to give the title object compound (2.24 g, 93%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.90 (s, 3 H), 7.40 (dd, J=8.2, 4.6 Hz, 1 H), 8.21 (dd, J=8.2, 1.4 Hz, 1 H), 8.79 (dd, J=4.6, 1.4 Hz, 1 H), 10.43 (s, 1 H).

[1425]

(3)cyclohexyl(3-methylthieno[3,2-b]pyridin-2-yl)methanone

To a solution (50 mL) of 3-methylthieno[3,2-b]pyridine-2-carbaldehyde (2.24 g) synthesized above in tetrahydrofuran was added a 1.0M solution (18.9 mL) of cyclohexylmagnesium bromide in tetrahydrofuran at 0°C, and the mixture was stirred at 0°C for 1.5 hr under argon atmosphere. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate,

and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 - 50% ethyl acetate/hexane) to give a pale-yellow oil. To a mixture of the obtained oil, 4-methylmorpholine N-oxide (1.81 g) and acetonitrile (40 mL) was added tetrapropylammonium perruthenate (238 mg), and the mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 30% ethyl acetate/hexane) to give the title object compound (1.38 g, 79%) as a colorless oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.19 - 1.65 (m, 5 H), 1.70 - 1.81 (m, 1 H), 1.82 - 1.94 (m, 2 H), 1.94 - 2.08 (m, 2 H), 2.86 (s, 3 H), 3.01 - 3.15 (m, 1 H), 7.37 (dd, J=8.2, 4.4 Hz, 1 H), 8.17 (dd, J=8.2, 1.5 Hz, 1 H), 8.78 (dd, J=4.4, 1.5 Hz, 1 H).
[1426]
(4) methyl 4-{[cyclohexyl(3-methylthieno[3,2-b]pyridin-2-yl)methyl]amino}benzoate

To a mixture of cyclohexyl(3-methylthieno[3,2-b]pyridin-2-yl)methanone (1.38 g) synthesized above, methyl 4-aminobenzoate (884 mg), triethylamine (5.94 mL) and methylene chloride (30 mL) was added titanium (IV) chloride (700 µL) at 0°C, and the mixture was stirred at room temperature for 3.5 days under argon atmosphere. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (30 mL) of the obtained oil in tetrahydrofuran were added acetic acid (607 µL) and sodium cyanoborohydride (666 mg), and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (10 - 50% ethyl acetate/hexane) to give the title object compound (1.31 g, 62%)as a brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.07 - 1.37 (m, 5 H), 1.55 - 1.90 (m, 5 H), 2.03 - 2.16 (m, 1 H), 2.59 (s, 3 H), 3.79 (s, 3 H), 4.56 (d, J=5.8 Hz, 1 H), 4.63 - 4.72 (m, 1 H), 6.51 (d, J=8.5 Hz, 2 H), 7.16 (dd, J=8.1, 4.6 Hz, 1 H), 7.77 (d, J=8.5 Hz, 2 H), 7.98 (dd, J=8.1, 1.2 Hz, 1 H), 8.64 (dd, J=4.6, 1.2 Hz, 1 H).

[1427]

(5)4-{[cyclohexyl(3-methylthieno[3,2-b]pyridin-2-yl)methyl]amino}benzoic acid

To a mixture of methyl 4-{[cyclohexyl(3-methylthieno[3,2-b]pyridin-2-yl)methyl]amino}benzoate (1.31 g) synthesized above, tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N aqueous sodium hydroxide solution (10 mL), and the mixture was stirred overnight with heating under reflux. 1N Aqueous sodium hydroxide solution (5 mL) was additionally added, and the mixture was further stirred with heating under reflux for 7 hr, and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (15 mL) was added at 0°C. The resulting precipitate was collected by filtration, and the obtained brown solid was dissolved in ethyl acetate. The solution was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title object compound (804 mg, 64%) as a brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.07 - 1.36 (m, 5 H), 1.55 - 1.91 (m, 5 H), 2.02 - 2.15 (m, 1 H), 2.60 (s, 3 H), 4.52 - 4.74 (m, 2 H), 6.52 (d, J=8.7 Hz, 2 H), 7.17 (dd, J=8.0, 4.6 Hz, 1 H), 7.82 (d, J=8.7 Hz, 2 H), 7.99 (dd, J=8.0, 1.4 Hz, 1 H), 8.66 (dd, J=4.6, 1.4 Hz, 1 H).

[1428]

(6) ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate

To a mixture of 4-{[cyclohexyl(3-methylthieno[3,2-b]pyridin-2-yl)methyl]amino}benzoic acid (300 mg) synthesized above, β-alanine ethyl ester hydrochloride (181 mg), 1-hydroxybenzotriazole monohydrate (181 mg), triethylamine (329 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (226 mg), and the mixture was stirred at room temperature for 1 day. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60 - 100% ethyl acetate/hexane) to give the title object compound (330 mg, 87%) as a pale-brown solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.07 - 1.36 (m, 8 H), 1.56 - 1.90 (m, 5 H), 2.02 - 2.16 (m, 1 H), 2.52 - 2.63 (m, 5 H), 3.59 - 3.68 (m, 2 H), 4.12 (q, J=7.1 Hz, 2 H), 4.49 (d, J=5.8 Hz, 1 H), 4.62 - 4.69 (m, 1 H), 6.52 (d, J=8.5 Hz, 2 H), 6.59 (t, J=5.8 Hz, 1 H), 7.16 (dd, J=8.1, 4.6 Hz, 1 H), 7.52 (d, J=8.5 Hz, 2 H), 7.99 (dd, J=8.1, 1.4 Hz, 1 H), 8.64 (dd, J=4.6, 1.4 Hz, 1 H).

[1429]

(7)3-{[(4-{[cyclohexyl(3-methylthieno[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate (330 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (291 mg, 94%) as a white

solid.

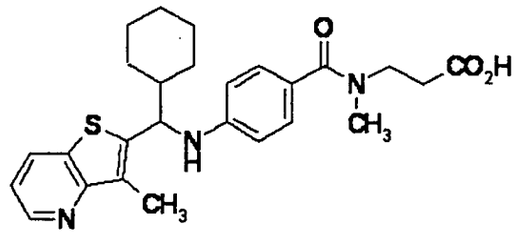
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.07 - 1.36 (m, 5 H), 1.55 - 1.89 (m, 5 H), 2.03 - 2.14 (m, 1 H), 2.57 (s, 3 H), 2.63 (t, J=5.7 Hz, 2 H), 3.55 - 3.77 (m, 2 H), 4.64 (d, J=7.2 Hz, 1 H), 6.49 (d, J=8.9 Hz, 2 H), 6.78 (t, J=6.0 Hz, 1 H), 7.19 (dd, J=8.0, 4.6 Hz, 1 H), 7.53 (d, J=8.9 Hz, 2 H), 8.01 (dd, J=8.0, 1.5 Hz, 1 H), 8.64 (dd, J=4.6, 1.5 Hz, 1 H).

[1430]

Example A145

3-{[(4-{[cyclohexyl(3-methylthieno[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1431]



[1432]

(1) ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 4-{[cyclohexyl(3-methylthieno[3,2-b]pyridin-2-yl)methyl]amino}benzoic acid (300 mg) synthesized in Example A144(5), ethyl 3-(methylamino)propanoate (155 mg), 1-hydroxybenzotriazole monohydrate (181 mg), triethylamine (329 μL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (226 mg), and the mixture was stirred at room temperature for 1 day. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50 - 100% ethyl acetate/hexane) to give the

title object compound (325 mg, 84%) as a pale-yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.07 - 1.36 (m, 8 H), 1.54 - 1.92 (m, 5 H), 2.01 - 2.16 (m, 1 H), 2.51 - 2.68 (m, 5 H), 2.99 (s, 3 H), 3.69 (t, J=7.0 Hz, 2 H), 4.10 (q, J=6.9 Hz, 2 H), 4.36 (d, J=5.2 Hz, 1 H), 4.58 - 4.67 (m, 1 H), 6.51 (d, J=8.5 Hz, 2 H), 7.13 - 7.23 (m, 3 H), 8.00 (d, J=8.0 Hz, 1 H), 8.64 (d, J=4.4 Hz, 1 H).

[1433]

(2)3-{[(4-{[cyclohexyl(3-methylthieno[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

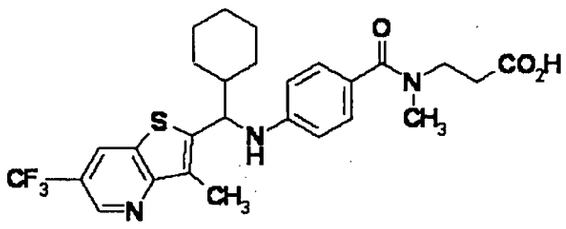
To a mixture of ethyl 3-{[(4-{[cyclohexyl(3-methylthieno[3,2-b]pyridin-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (325 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (277 mg, 90%) as a white solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.06 - 1.34 (m, 5 H), 1.55 - 1.88 (m, 5 H), 2.03 - 2.15 (m, 1 H), 2.58 (s, 3 H), 2.66 (t, J=6.3 Hz, 2 H), 3.02 (s, 3 H), 3.70 (t, J=6.3 Hz, 2 H), 4.62 (d, J=7.5 Hz, 1 H), 6.50 (d, J=8.7 Hz, 2 H), 7.15 - 7.25 (m, 3 H), 8.01 (dd, J=8.3, 1.5 Hz, 1 H), 8.66 (dd, J=4.5, 1.5 Hz, 1 H).

[1434]

Example A146

3-[{[4-({cyclohexyl[3-methyl-6-(trifluoromethyl)thieno[3,2-b]pyridin-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1435]



[1436]

(1) ethyl 3-methyl-6-(trifluoromethyl)thieno[3,2-b]pyridine-2-carboxylate

To a solution (50 mL) of 3-chloro-5-(trifluoromethyl)pyridine-2-carbonitrile (5.00 g) in tetrahydrofuran was added 3.0M solution (16.1 mL) of methylmagnesium bromide in diethyl ether at 0°C, and the mixture was stirred for 3 hr under argon atmosphere. To the reaction mixture was added 1N hydrochloric acid (300 mL) to acidify the solution to pH=3 - 4, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 10% ethyl acetate/hexane) to give a pale-yellow solid. To a mixture of the obtained solid, ethyl mercaptoacetate (1.61 mL) and N,N-dimethylformamide (30 mL) was added potassium carbonate (5.56 g), and the mixture was stirred at 50°C for 10 hr. Water was added to quench the reaction, and the precipitated solid was collected by filtration to give the title object compound (3.76 g, 54%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.45 (t, J=7.1 Hz, 3 H), 2.88 (s, 3 H), 4.45 (q, J=7.1 Hz, 2 H), 8.39 - 8.45 (m, 1 H), 8.94 - 9.02 (m, 1 H).

[1437]

(2)3-methyl-6-(trifluoromethyl)thieno[3,2-b]pyridine-2-carbaldehyde

To a mixture of ethyl 3-methyl-6-(trifluoromethyl)thieno[3,2-b]pyridine-2-carboxylate (3.69 g)

synthesized above, calcium chloride (2.84 g), ethanol (40 mL) and tetrahydrofuran (40 mL) was added sodium borohydride (1.94 g) at 0°C, and the mixture was stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a white solid. To a solution (60 mL) of the obtained solid in tetrahydrofuran was added active manganese dioxide (16.3 g), and the mixture was stirred at 50°C for 5 hr. Manganese dioxide was filtered off, and the filtrate was concentrated under reduced pressure to give the title object compound (2.88 g, 92%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.93 (s, 3 H), 8.47 - 8.50 (m, 1 H), 9.00 (d, J=1.6 Hz, 1 H), 10.46 (s, 1 H).

[1438]

(3)cyclohexyl[3-methyl-6-(trifluoromethyl)thieno[3,2-b]pyridin-2-yl]methanone

To a solution (15 mL) of 3-methyl-6-(trifluoromethyl)thieno[3,2-b]pyridine-2-carbaldehyde (1.44 g) synthesized above in tetrahydrofuran was added 1.0M solution (8.81 mL) of cyclohexylmagnesium bromide in tetrahydrofuran at 0°C, and the mixture was stirred for 1 hr under argon atmosphere. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 - 50% ethyl acetate/hexane) to give a yellow oil. To a mixture of the obtained oil, 4-methylmorpholine N-oxide (817 mg) and acetonitrile (20 mL) was added tetrapropylammonium perruthenate (108 mg), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (0 - 10% ethyl acetate/hexane) to give the title object compound (805 mg, 42%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.19 - 1.65 (m, 5 H), 1.70 - 1.81 (m, 1 H), 1.82 - 2.07 (m, 4 H), 2.86 (s, 3 H), 3.01 - 3.15 (m, 1 H), 8.42 (s, 1 H), 8.98 (s, 1 H).

[1439]

(4) methyl 4-({cyclohexyl[3-methyl-6-(trifluoromethyl)thieno[3,2-b]pyridin-2-yl]methyl}amino)benzoate

To a mixture of cyclohexyl[3-methyl-6-(trifluoromethyl)thieno[3,2-b]pyridin-2-yl]methanone (805 mg) synthesized above, methyl 4-aminobenzoate (410 mg), triethylamine (2.75 mL) and methylene chloride (10 mL) was added titanium (IV) chloride (323 μL) at 0°C, and the mixture was stirred at room temperature for 1 day under argon atmosphere. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown oil. To a solution (10 mL) of the obtained oil in tetrahydrofuran were added acetic acid (282 μL) and sodium cyanoborohydride (309 mg), and the mixture was stirred at room temperature for 1 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 40% ethyl acetate/hexane) to give the title object compound (775 mg, 68%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.05 - 1.36 (m, 5 H), 1.53 - 1.91 (m, 5 H), 2.02 - 2.15 (m, 1 H), 2.62 (s, 3 H), 3.79 (s, 3 H), 4.58 (d, J=5.5 Hz, 1 H), 4.66 - 4.74 (m, 1 H), 6.50 (d, J=8.8

635

Hz, 2 H), 7.77 (d, J=8.8 Hz, 2 H), 8.23 (d, J=1.3 Hz, 1 H), 8.87 (d, J=1.3 Hz, 1 H).

[1440]

(5) 4-({cyclohexyl[3-methyl-6-(trifluoromethyl)thieno[3,2-b]pyridin-2-yl]methyl}amino)benzoic acid

To a mixture of methyl 4-({cyclohexyl[3-methyl-6-(trifluoromethyl)thieno[3,2-b]pyridin-2-yl]methyl}amino)benzoate (775 mg) synthesized above, tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N aqueous sodium hydroxide solution (10 mL), and the mixture was stirred for 1 day with heating under reflux, and concentrated under reduced pressure. The residue was dissolved in water (20 mL), and 1N hydrochloric acid (10 mL) was added at 0°C, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (671 mg, 87%) as a pale-brown solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.07 - 1.38 (m, 5 H), 1.53 - 1.93 (m, 5 H), 2.00 - 2.14 (m, 1 H), 2.62 (s, 3 H), 4.55 - 4.80 (m, 2 H), 6.50 (d, J=8.8 Hz, 2 H), 7.82 (d, J=8.8 Hz, 2 H), 8.23 (d, J=1.3 Hz, 1 H), 8.88 (d, J=1.3 Hz, 1 H).

[1441]

(6) ethyl 3-[{[4-({cyclohexyl[3-methyl-6-(trifluoromethyl)thieno[3,2-b]pyridin-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

To a mixture of 4-({cyclohexyl[3-methyl-6-(trifluoromethyl)thieno[3,2-b]pyridin-2-yl]methyl}amino)benzoic acid (343 mg) synthesized above, ethyl 3-(methylamino)propanoate (151 mg), 1-hydroxybenzotriazole monohydrate (176 mg), triethylamine (321 µL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (221 mg), and the mixture was stirred at room temperature for 2.5 days.

Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (310 mg, 72%) as a white solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.08 - 1.35 (m, 8 H), 1.54 - 1.92 (m, 5 H), 2.01 - 2.13 (m, 1 H), 2.51 - 2.68 (m, 5 H), 2.99 (s, 3 H), 3.69 (t, J=7.0 Hz, 2 H), 4.10 (q, J=7.1 Hz, 2 H), 4.37 - 4.46 (m, 1 H), 4.60 - 4.68 (m, 1 H), 6.49 (d, J=8.7 Hz, 2 H), 7.19 (d, J=8.7 Hz, 2 H), 8.24 (s, 1 H), 8.87 (s, 1 H).

[1442]

(7)3-[{[4-({cyclohexyl[3-methyl-6-(trifluoromethyl)thieno[3,2-b]pyridin-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a mixture of ethyl 3-[{[4-({cyclohexyl[3-methyl-6-(trifluoromethyl)thieno[3,2-b]pyridin-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (310 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (284 mg, 96%) as a white solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.07 - 1.35 (m, 5 H), 1.53 - 1.89 (m, 5 H), 2.00 - 2.12 (m, 1 H), 2.54 - 2.69 (m, 5 H), 3.00 (s, 3 H), 3.68 (t, J=6.6 Hz, 2 H), 4.64 (d, J=7.2 Hz, 1 H), 6.49 (d, J=8.3 Hz, 2 H), 7.20 (d, J=8.3 Hz, 2 H), 8.25 (s, 1 H), 8.88 (s, 1 H).

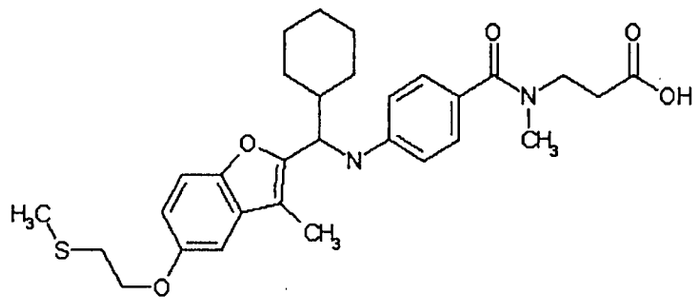
[1443]

Example A147

3-[({4-[(cyclohexyl{3-methyl-5-[2-(methylthio)ethoxy]-1-benzofuran-2-

yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[1444]



[1445]

(1)cyclohexyl{3-methyl-5-[2-(methylsulfanyl)ethoxy]-1-benzofuran-2-yl}methanone

Cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methanone (0.76 g) synthesized in Example A82(3) was dissolved in tetrahydrofuran (15 mL), and 2-(methylthio)ethanol (0.26 mL), tributylphosphine (1.5 mL) and 1,1'-(azodicarbonyl)dipiperidine (1.46 g) were added to the solution under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 12 hr. Hexane (15 mL) was added to the mixture, and the precipitate was filtered off through celite. Water was added to the filtrate, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (0.73 g, 76%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.18 - 2.01 (m, 10 H), 2.24 (s, 3 H), 2.57 (s, 3 H), 2.92 (t, J=6.8 Hz, 2 H), 3.25 - 3.40 (m, 1 H), 4.21 (t, J=6.8 Hz, 2 H), 7.03 - 7.41 (m, 3 H).

[1446]

(2)cyclohexyl{3-methyl-5-[2-(methylsulfanyl)ethoxy]-1-benzofuran-2-yl}methanol

Cyclohexyl{3-methyl-5-[2-(methylsulfanyl)ethoxy]-1-benzofuran-2-yl}methanone (0.73 g) synthesized in the above-

mentioned (1) was dissolved in a tetrahydrofuran (10 mL) and methanol (5 mL), and sodium borohydride (90%, 0.18 g) was added to the solution under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr. The mixture was ice-cooled again, water (1 mL) and 1N hydrochloric acid (5 mL) were carefully added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (0.67 g, 91%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 - 1.99 (m, 11 H), 2.19 (s, 3 H), 2.23 (s, 3 H), 2.91 (t, J=6.9 Hz, 2 H), 4.20 (t, J=6.9 Hz, 2 H), 4.51 (dd, J=8.5, 6.0 Hz, 1 H), 6.79 - 6.98 (m, 2 H), 7.31 (d, J=9.0 Hz, 1 H).

[1447]

(3) ethyl 3-[({4-[(cyclohexyl{3-methyl-5-[2-(methylsulfanyl)ethoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate

Cyclohexyl{3-methyl-5-[2-(methylsulfanyl)ethoxy]-1-benzofuran-2-yl}methanol (0.34 g) synthesized in the above-mentioned (2) was dissolved in tetrahydrofuran (5 mL), and thionyl chloride (0.13 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (10 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (5 mL), sodium iodide (0.23 g), sodium carbonate (0.15 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.25 g) synthesized in Example 2(2) were added to the solution, and

the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (0.33 g, 59%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 2.00 (m, 15 H), 2.05 (s, 3 H), 2.22 (s, 3 H), 2.61 (t, J=6.8 Hz, 2 H), 2.89 (t, J=6.9 Hz, 2 H), 3.01 (s, 3 H), 3.70 (t, J=6.8 Hz, 2 H), 4.00 - 4.20 (m, 4 H), 4.36 (d, J=8.0 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.78 - 6.94 (m, 2 H), 7.14 - 7.25 (m, 3 H).

[1448]

(4)3-[({4-[(cyclohexyl{3-methyl-5-[2-(methylthio)ethoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

Ethyl 3-[({4-[(cyclohexyl{3-methyl-5-[2-(methylsulfanyl)ethoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate (0.33 g) synthesized in the above-mentioned (3) was dissolved in ethanol (2 mL), 1N aqueous sodium hydroxide solution (1.5 mL) was added to the solution at room temperature, and the mixture was stirred at 50°C for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (1.5 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethanol-water to give the title object compound (0.20 g, 63%) as a colorless solid.

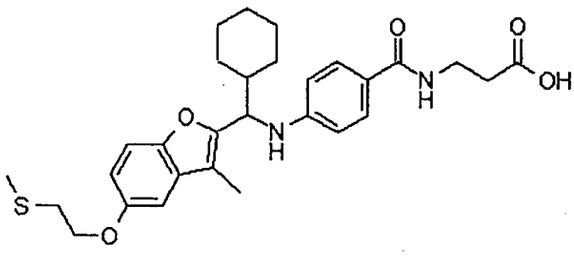
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.88 - 2.11 (m, 12 H), 2.15 (s, 3 H), 2.23 (s, 3 H), 2.40 - 2.46 (m, 2 H), 2.76 - 2.96 (m, 5 H), 3.50 (t, J=7.3 Hz, 2 H), 4.15 (t, J=6.7 Hz, 2 H), 4.37 (t, J=8.3 Hz, 1 H), 6.46 (d, J=8.1 Hz, 1 H), 6.59 (d, J=8.7 Hz, 2 H), 6.80 (dd, J=8.7, 2.6 Hz, 1 H), 7.03 (d, J=2.6 Hz, 1 H), 7.09 (d, J=8.7 Hz, 2 H), 7.32 (d, J=8.7 Hz, 1 H).

[1449]

Example A148

3-[({4-[(cyclohexyl{3-methyl-5-[2-(methylthio)ethoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[1450]



[1451]

Cyclohexyl{3-methyl-5-[2-(methylsulfanyl)ethoxy]-1-benzofuran-2-yl}methanol synthesized in Example A147(2) was dissolved in tetrahydrofuran (5 mL), and thionyl chloride (0.13 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (10 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (5 mL), sodium iodide (0.23 g), sodium carbonate (0.15 g) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.25 g) synthesized in Example 1(2) were added, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (0.38 g, 69%) as a yellow oil. This was dissolved in ethanol (2 mL), 1N aqueous sodium

hydroxide solution (1.5 mL) was added to the solution at room temperature, and the mixture was stirred at 50°C for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (1.5 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethanol-water to give the title object compound (0.18 g, 49%) as a colorless solid.

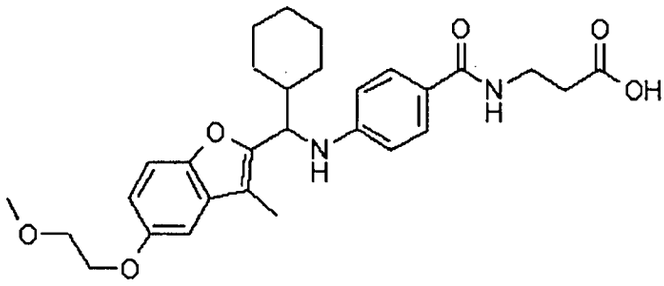
$^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.88 - 2.10 (m, 12 H), 2.15 (s, 3 H), 2.23 (s, 3 H), 2.42 (t, J=7.2 Hz, 2 H), 2.84 (t, J=6.5 Hz, 2 H), 3.47 - 3.55 (m, 2 H), 4.15 (t, J=6.6 Hz, 2 H), 4.41 (t, J=8.4 Hz, 1 H), 6.49 - 6.64 (m, 3 H), 6.79 (dd, J=8.9, 2.5 Hz, 1 H), 7.03 (d, J=2.4 Hz, 1 H), 7.32 (d, J=8.9 Hz, 1 H), 7.51 (d, J=8.7 Hz, 2 H), 7.99 (t, J=5.5 Hz, 1 H).

[1452]

Example A149

3-[{[4-({cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}amino]propanoic acid

[1453]



[1454]

To a solution (15 mL) of cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methanol (0.86 g) synthesized in Example A79(3) in tetrahydrofuran was added thionyl chloride (0.35 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (20 mL) was carefully added. The reaction mixture was stirred for 10

min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (15 mL), sodium iodide (0.61 g), sodium carbonate (0.41 g) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.64 g) synthesized in Example 1(2) were added to the solution, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}amino]propanoate (0.62 g, 43%) as a yellow oil. This was dissolved in ethanol (5 mL), 1N aqueous sodium hydroxide solution (3.0 mL) was added to the solution at room temperature, and the mixture was stirred at 50°C for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (3.0 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethanol-water to give the title object compound (0.54 g, 91%) as a colorless solid.

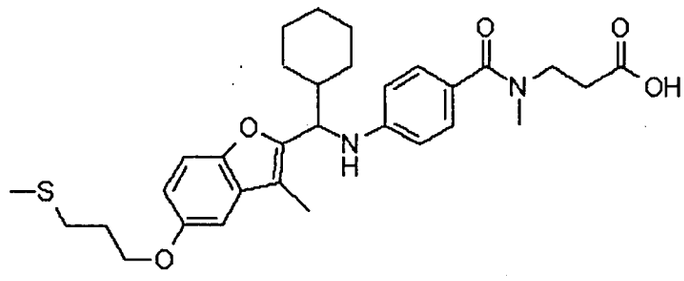
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 2.13 (m, 12 H), 2.21 (s, 3 H), 2.66 (t, J=5.7 Hz, 2 H), 3.46 (s, 3 H), 3.58 - 3.71 (m, 2 H), 3.76 (dd, J=5.6, 4.1 Hz, 2 H), 4.14 (dd, J=5.7, 4.1 Hz, 2 H), 4.38 (d, J=7.9 Hz, 1 H), 6.57 - 6.65 (m, 3 H), 6.80 - 6.98 (m, 2 H), 7.22 - 7.26 (m, 1H), 7.53 (d, J=8.7 Hz, 2 H).

[1455]

Example A150

3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfanyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[1456]



[1457]

(1)cyclohexyl{3-methyl-5-[3-(methylsulfanyl)propoxy]-1-benzofuran-2-yl}methanone

Cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methanone (2.4 g) synthesized in Example A82(3) was dissolved in tetrahydrofuran (50 mL), and 2-(methylthio)propanol (1.0 mL), tributylphosphine (4.7 mL) and 1,1'-(azodicarbonyl)dipiperidine (4.7 g) were added to the solution under ice-cooling. The ice bath was removed and the reaction mixture was stirred at room temperature for 12 hr. Hexane (50 mL) was added to the mixture, and the precipitate was filtered off through celite. Water was added to the filtrate, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (3.1 g, 95%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.18 - 2.01 (m, 12 H), 2.14 (s, 3 H), 2.56 (s, 3 H), 2.72 (t, J=7.2 Hz, 2 H), 3.25 - 3.40 (m, 1 H), 4.08 - 4.20 (m, 2 H), 7.03 - 7.42 (m, 3 H).

[1458]

(2)cyclohexyl{3-methyl-5-[3-(methylsulfanyl)propoxy]-1-benzofuran-2-yl}methanol

Cyclohexyl{3-methyl-5-[3-(methylsulfanyl)propoxy]-1-benzofuran-2-yl}methanone (3.1 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (50 mL) and methanol (10 mL), and sodium borohydride (90%, 0.73 g) was added to the solution under ice-cooling. The ice bath was

removed, the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (5 mL) and 1N hydrochloric acid (25 mL) were carefully added to the mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (3.0 g, 95%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.18 - 2.01 (m, 14 H), 2.13 (s, 3 H), 2.19 (s, 3 H), 2.72 (t, J=7.2 Hz, 2 H), 4.11 (t, J=7.2 Hz, 2 H), 4.40 - 4.55 (m, 1 H), 6.80 - 7.42 (m, 3 H).

[1459]

(3) ethyl 3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfanyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate

Cyclohexyl{3-methyl-5-[3-(methylsulfanyl)propoxy]-1-benzofuran-2-yl}methanol (1.5 g) synthesized in the above-mentioned (2) was dissolved in tetrahydrofuran (10 mL), and thionyl chloride (0.56 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (30 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (10 mL), sodium iodide (0.95 g), sodium carbonate (0.63 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (1.1 g) synthesized in Example 2(2) were added to the solution, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica

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gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (1.4 g, 56%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 2.00 (m, 17 H), 2.12 (s, 3 H), 2.21 (s, 3 H), 2.52 - 2.79 (m, 4 H), 3.01 (s, 3 H), 3.70 (t, J=7.2 Hz, 2 H), 4.00 - 4.36 (m, 5 H), 6.56 (d, J=8.7 Hz, 2 H), 6.78 - 6.94 (m, 2 H), 7.14 - 7.25 (m, 3 H).

[1460]

(4)3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfanyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

Ethyl 3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfanyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate (0.37 g) synthesized in the above-mentioned (3) was dissolved in ethanol (5 mL), 1N aqueous sodium hydroxide solution (2.0 mL) was added to the solution at room temperature, and the mixture was stirred at 50°C for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (2.0 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethanol-water to give the title object compound (0.28 g, 79%) as a colorless solid.

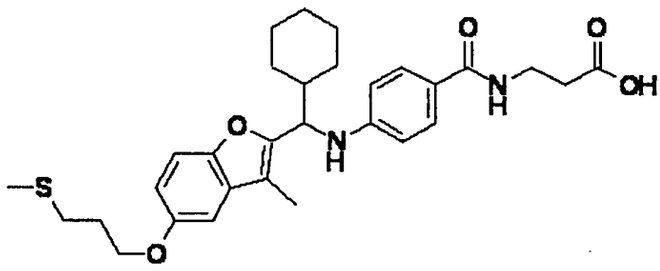
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.89 - 2.10 (m, 14 H), 2.12 (s, 3 H), 2.21 (s, 3 H), 2.52 - 2.81 (m, 4 H), 3.04 (s, 3 H), 3.70 (q, J=6.4 Hz, 2 H), 4.09 (t, J=6.4 Hz, 2 H), 4.36 (d, J=7.9 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.77 - 6.96 (m, 2 H), 7.20 - 7.26 (m, 3 H).

[1461]

Example A151

3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfanyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[1462]



[1463]

(1) ethyl 3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfanyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoate

Cyclohexyl{3-methyl-5-[3-(methylsulfanyl)propoxy]-1-benzofuran-2-yl}methanol (1.5 g) synthesized in Example A150(2) was dissolved in tetrahydrofuran (10 mL), and thionyl chloride (0.56 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (30 mL) was carefully added. The reaction mixture was stirred for 10 min, and extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (10 mL), sodium iodide (0.95 g), sodium carbonate (0.63 g) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (1.0 g) synthesized in Example 1(2) were added to the solution, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (1.8 g, 77%) as a yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 2.00 (m, 17 H), 2.12 (s, 3 H), 2.21 (s, 3 H), 2.52 - 2.79 (m, 4 H), 3.66 (q J=6.0 Hz, 2 H), 4.00 - 4.60 (m, 5 H), 6.56 (d, J=8.9 Hz, 2 H), 6.58 (br. s. 1 H), 6.78 - 6.94 (m, 2 H), 7.20 - 7.60 (m, 3 H).

[1464]

(2)3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfanyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

Ethyl 3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfanyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoate (0.25 g) synthesized in the above-mentioned (1) was dissolved in ethanol (5 mL), 1N aqueous sodium hydroxide solution (2.0 mL) was added to the solution at room temperature, and the mixture was stirred at 50°C for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (2.0 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethanol-water to give the title object compound (0.07 g, 31%) as a colorless solid.

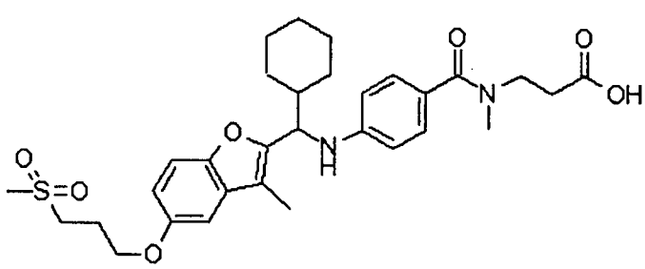
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.82 - 2.16 (m, 14 H), 2.22 (s, 3 H), 2.52 - 2.81 (m, 4 H), 3.66 (q, J=6.0 Hz, 2 H), 4.08 (t, J=6.0 Hz, 2 H), 4.38 (d, J=7.9 Hz, 1 H), 6.43 - 6.66 (m, 3 H), 6.74 - 6.96 (m, 2 H), 7.20 - 7.26 (m, 1 H), 7.53 (d, J=8.9 Hz, 2 H).

[1465]

Example A152

3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfonyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[1466]



[1467]

(1) ethyl 3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfonyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate

Ethyl 3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfanyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate (0.61 g) synthesized in Example A150(3) was dissolved in methanol (15 mL) and water (2 mL), oxone (2.1 g) was added to the solution at room temperature, and the mixture was stirred for 30 min. Water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (0.48 g, 75%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 2.01 (m, 17 H), 2.21 (s, 3 H), 2.28 - 2.42 (m, 2 H), 2.61 (t, J=6.9 Hz, 2 H), 2.95 (s, 3 H), 3.01 (s, 3 H), 3.20 - 3.36 (m, 2 H), 3.70 (t, J=6.9 Hz, 2 H), 4.04 - 4.19 (m, 2 H), 4.26 - 4.44 (m, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.74 - 6.91 (m, 2 H), 7.15 - 7.25 (m, 3 H).

[1468]

(2)3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfonyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

Ethyl 3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfonyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate (0.48 g) synthesized in the above-mentioned (1) was dissolved in ethanol (5 mL), 1N aqueous sodium hydroxide solution (1.5 mL) was added to the solution at room temperature, and the mixture was stirred at 50°C for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (1.5 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure.

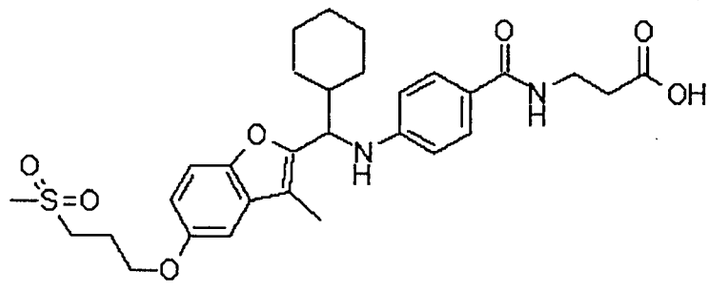
The residue was washed with ethanol-water to give the title object compound (0.35 g, 78%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.87 - 2.15 (m, 12 H), 2.21 (s, 3 H), 2.25 - 2.45 (m, 2 H), 2.67 (br. s., 2 H), 2.95 (s, 3 H), 3.04 (s, 3 H), 3.17 - 3.36 (m, 2 H), 3.69 (t, J=6.5 Hz, 2 H), 4.13 (t, J=5.7 Hz, 2 H), 4.36 (d, J=7.9 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.70 - 6.93 (m, 2 H), 7.16 - 7.26 (m, 3 H).

[1469]

Example A153

3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfonyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[1470]



[1471]

(1) ethyl 3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfonyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoate

Ethyl 3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfanyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoate (0.16 g) synthesized in Example A151(1) was dissolved in acetone (5 mL), metachloroperbenzoic acid (0.2 g) was added to the solution under ice-cooling, and the mixture was stirred for 15 min. To the reaction mixture was added sodium sulfite aqueous solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object

compound (0.11 g, 68%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.89 - 1.92 (m, 17 H), 2.22 (s, 3 H), 2.25 - 2.44 (m, 2 H), 2.58 (t, J=5.8 Hz, 2 H), 2.95 (s, 3 H), 3.14 - 3.35 (m, 2 H), 3.66 (q, J=6.8 Hz, 2 H), 4.13 (q, J=7.2 Hz, 2 H), 4.38 (d, J=7.9 Hz, 1 H), 6.43 - 6.64 (m, 3 H), 6.73 - 6.90 (m, 2 H), 7.16 - 7.25 (m, 1 H), 7.54 (d, J=8.7 Hz, 2 H).

[1472]

(2)3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfonyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

Ethyl 3-[({4-[(cyclohexyl{3-methyl-5-[3-(methylsulfonyl)propoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoate (0.11 g) synthesized in the above-mentioned (1) was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at 50°C for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (1.0 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethanol-water to give the title object compound (0.9 g, 80%) as a colorless solid.

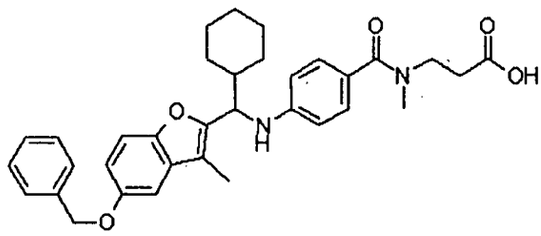
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 2.14 (m, 14 H), 2.22 (s, 3 H), 2.26 - 2.42 (m, 2 H), 2.60 - 2.72 (m, 2 H), 2.95 (s, 3 H), 3.17 - 3.33 (m, 2 H), 3.66 (q, J=5.7 Hz, 2 H), 4.13 (t, J=5.7 Hz, 2 H), 4.38 (d, J=7.9 Hz, 1 H), 6.47 - 6.62 (m, 3 H), 6.74 - 6.90 (m, 2 H), 7.20 - 7.26 (m, 1 H), 7.53 (d, J=8.7 Hz, 2 H).

[1473]

Example A154

3-[{[4-({[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoic acid

[1474]



[1475]

(1) [5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methanol

1-[5-(Benzyloxy)-2-hydroxyphenyl]ethanone (1.5 g) synthesized in Example A82(2) was dissolved in tetrahydrofuran (25 mL) and methanol (5 mL), and sodium borohydride (90%, 0.36 g) was added to the solution under ice-cooling. The ice bath was removed, the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (5 mL) and 1N hydrochloric acid (10 mL) were carefully added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (1.4 g, 95%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.81 - 2.00 (m, 12 H), 2.18 (s, 3 H), 4.51 (d, J=8.3 Hz, 1 H), 5.10 (s, 2 H), 6.87 - 7.06 (m, 2 H), 7.29 - 7.58 (m, 6 H).

[1476]

(2) ethyl 3-[{[4-({[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoate

[5-(Benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methanol (1.5 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (20 mL), and thionyl chloride (0.57 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous

sodium hydrogen carbonate solution (30 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (15 mL), sodium iodide (0.98 g), sodium carbonate (0.65 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (1.1 g) synthesized in Example 2(2) were added, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (1.8 g, 72%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 - 2.00 (m, 15 H), 2.21 (s, 3 H), 2.61 (t, J=7.1 Hz, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.1 Hz, 2 H), 4.12 (q, J=7.2 Hz, 2 H), 4.27 - 4.43 (m, 2 H), 5.08 (s, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.79 - 7.01 (m, 2 H), 7.13 - 7.24 (m, 3 H), 7.30 - 7.59 (m, 5 H).

[1477]

(3)3-[{[4-({[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoic acid

Ethyl 3-[{[4-({[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoate (0.2 g) synthesized in the above-mentioned (2) was dissolved in ethanol (5 mL), 1N aqueous sodium hydroxide solution (1.5 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (1.5 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed

with ethanol-water to give the title object compound (0.18 g, 94%) as a colorless solid.

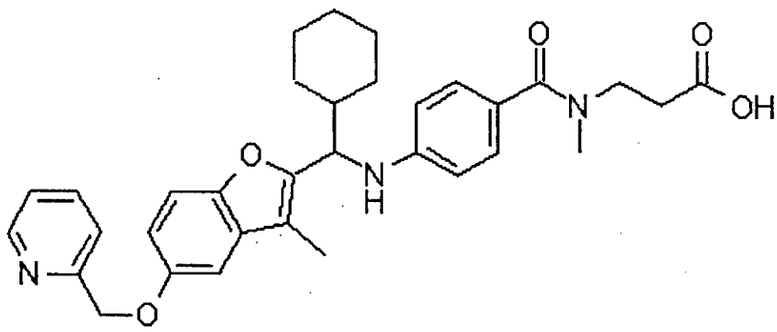
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.79 - 2.14 (m, 12 H), 2.21 (s, 3 H), 2.63 (t, J=6.2 Hz, 2 H), 3.01 (s, 3 H), 3.68 (t, J=6.2 Hz, 2 H), 4.36 (d, J=7.9 Hz, 1 H), 5.08 (s, 2 H), 6.55 (d, J=8.7 Hz, 2 H), 6.80 - 7.03 (m, 2 H), 7.13 - 7.52 (m, 8 H).

[1478]

Example A155

3-[{[4-({cyclohexyl[3-methyl-5-(pyridin-2-ylmethoxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1479]



[1480]

(1) ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

Ethyl 3-[{[4-({[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoate (2.46 g) synthesized in Example A154(2) was dissolved in ethanol (50 mL), and platinum oxide (0.33 g) was added to the solution. The reaction mixture was stirred under hydrogen atmosphere (1 atm) at room temperature overnight. The reaction mixture was filtered, and the residue was washed with ethanol. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (1.64 g, 79%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 - 1.91 (m, 15 H), 2.18 (s, 3

H), 2.61 (t, J=7.1 Hz, 2 H), 3.01 (s, 3 H), 3.71 (t, J=7.1 Hz, 2 H), 4.02 - 4.18 (m, 2 H), 4.28 - 4.41 (m, 1 H), 4.86 (s, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.66 - 6.87 (m, 2 H), 7.14 - 7.25 (m, 3 H).

[1481]

(2) ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(pyridin-2-ylmethoxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

Ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.23 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (5 mL), and 2-pyridinemethanol (62 mg), tributylphosphine (0.21 mL) and 1,1'-(azodicarbonyl)dipiperidine (0.21 g) were added to the solution under ice-cooling. The ice bath was removed, the reaction mixture was stirred at room temperature for 12 hr, then hexane (15 mL) was added to the mixture, and the precipitate was filtered off through celite. Water was added to the filtrate, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (0.19 g, 70%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.88 - 1.95 (m, 15 H), 2.21 (s, 3 H), 2.54 - 2.72 (m, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.2 Hz, 2 H), 4.01 - 4.21 (m, 2 H), 4.22 - 4.54 (m, 1 H), 5.10 (s, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.80 - 7.05 (m, 2 H), 7.21 (d, J=8.7 Hz, 2 H), 7.28 - 7.40 (m, 2 H), 7.79 (d, J=8.0 Hz, 1 H), 8.58 (d, J=4.5 Hz, 1 H), 8.70 (s, 1 H).

[1482]

(3)3-[{[4-({cyclohexyl[3-methyl-5-(pyridin-2-ylmethoxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

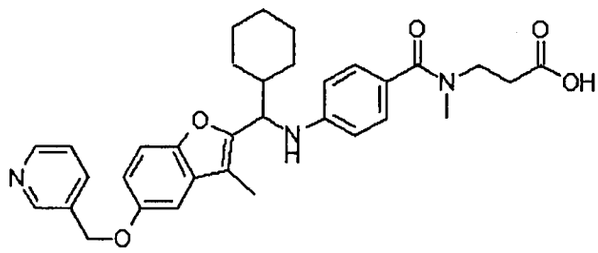
Ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(pyridin-2-ylmethoxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.19 g) synthesized in the above-mentioned (2) was dissolved in ethanol (5 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (1.0 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethanol-water to give the title object compound (0.11 g, 41%) as a yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 2.16 (m, 12 H), 2.20 (s, 3 H), 2.62 (br. s., 2 H), 3.02 (s, 3 H), 3.65 (br. s., 2 H), 4.34 (d, J=7.9 Hz, 1 H), 5.15 (s, 2 H), 6.54 (d, J=8.3 Hz, 2 H), 6.75 - 6.98 (m, 2 H), 7.11 - 7.30 (m, 4 H), 7.35 - 7.52 (m, 1 H), 7.93 (d, J=7.9 Hz, 1 H), 8.50 - 8.70 (m, 2 H).

[1483]

Example A156

3-[{[4-({cyclohexyl[3-methyl-5-(pyridin-3-ylmethoxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1484]



[1485]

(1) ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(pyridin-3-ylmethoxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

Ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-

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benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.23 g) synthesized in Example A155(1) was dissolved in tetrahydrofuran (5 mL), and 3-pyridinemethanol (62 mg), tributylphosphine (0.21 mL) and 1,1'-(azodicarbonyl)dipiperidine (0.21 g) were added to the solution under ice-cooling. The ice bath was removed, the reaction mixture was stirred at room temperature for 12 hr, then hexane (5 mL) was added to the mixture, and the precipitate was filtered off through celite. Water was added to the filtrate and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (0.13 g, 49%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 - 1.95 (m, 15 H), 2.19 (s, 3 H), 2.61 (br. s., 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.2 Hz, 2 H), 4.12 (q, J=7.2, 2.8 Hz, 2 H), 4.25 - 4.45 (m, 2 H), 5.24 (s, 2 H), 6.55 (d, J=8.7 Hz, 2 H), 6.84 - 7.02 (m, 2 H), 7.13 - 7.30 (m, 4 H), 7.55 (d, J=7.9 Hz, 1 H), 7.67 - 7.82 (m, 1 H), 8.48 - 8.71 (m, 1 H).

[1486]

(2)3-[{[4-({cyclohexyl[3-methyl-5-(pyridin-3-ylmethoxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

Ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(pyridin-3-ylmethoxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.13 g) synthesized in the above-mentioned (1) was dissolved in ethanol (5 mL), 1N aqueous sodium hydroxide solution (3.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (3.0 mL) was added to the residue, and the mixture was extracted

with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethanol-water to give the title object compound (0.08 g, 95%) as a pale-yellow solid.

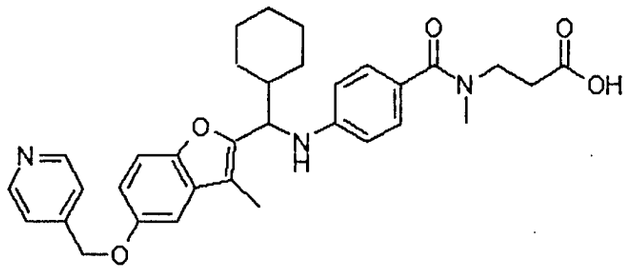
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.83 - 2.13 (m, 12 H), 2.18 (s, 3 H), 2.50-2.75 (br. s., 2H), 3.01 (s, 3 H), 3.64 (br. s., 2 H), 4.35 (d, J=7.9 Hz, 1 H), 5.44 (s, 2 H), 6.55 (d, J=8.7 Hz, 2 H), 6.79 - 7.09 (m, 2 H), 7.12 - 7.25 (m, 3 H), 7.45 - 8.01 (m, 3 H), 8.66 (br. s., 1 H).

[1487]

Example A157

3-[{[4-({cyclohexyl[3-methyl-5-(pyridin-4-ylmethoxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1488]



[1489]

(1) ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(pyridin-4-ylmethoxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

Ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.23 g) synthesized in Example A155(1) was dissolved in tetrahydrofuran (5 mL), and 4-pyridinemethanol (62 mg), tributylphosphine (0.21 mL) and 1,1'-(azodicarbonyl)dipiperidine (0.21 g) were added to the solution under ice-cooling. The ice bath was removed, the reaction mixture was stirred at room temperature for 12 hr,

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then hexane (5 mL) was added to the mixture, and the precipitate was filtered off through celite. Water was added to the filtrate, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (0.18 g, 64%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.89 - 1.97 (m, 15 H), 2.20 (s, 3 H), 2.61 (t, J=7.2 Hz, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.2 Hz, 2 H), 4.06 - 4.18 (q, J=7.2 Hz, 2 H), 4.74 (d, J=4.0 Hz, 1 H), 5.11 (s, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.82 - 6.99 (m, 2 H), 7.14 - 7.31 (m, 3 H), 7.38 (d, J=6.0 Hz, 2 H), 8.60 - 8.69 (m, 2 H).

[1490]

(2)3-[{[4-({cyclohexyl[3-methyl-5-(pyridin-4-ylmethoxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

Ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(pyridin-4-ylmethoxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.17 g) synthesized in the above-mentioned (1) was dissolved in ethanol (5 mL), 1N aqueous sodium hydroxide solution (3.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (3.0 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethanol-water to give the title object compound (0.13 g, 77%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.81 - 2.13 (m, 12 H), 2.19 (s, 3 H), 2.50-2.75 (br. s., 2H), 3.03 (s, 3 H), 3.60 - 3.75 (m, 2 H), 4.34 (d, J=7.9 Hz, 1 H), 5.16 (s, 2 H), 6.53 (d, J=8.5 Hz,

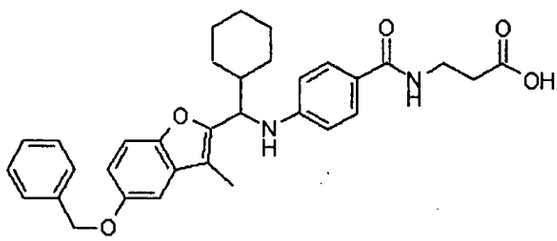
2 H), 6.78 - 6.97 (m, 2 H), 7.12 - 7.31 (m, 3 H), 7.44 (d, J=5.8 Hz, 2 H), 8.60 (d, J=5.8 Hz, 2 H).

[1491]

Example A158

3-({[4-({[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}amino)propanoic acid

[1492]



[1493]

(1) ethyl 3-({[4-({[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}amino)propanoate

[5-(Benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methanol (1.0 g) synthesized in Example A154(1) was dissolved in tetrahydrofuran (15 mL), and thionyl chloride (0.38 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (30 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (20 mL), sodium iodide (0.65 g), sodium carbonate (0.43 g) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.68 g) synthesized in Example 1(2) were added to the solution, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced

pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (0.78 g, 48%) as a yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 - 1.98 (m, 15 H), 2.21 (s, 3 H), 2.58 (t, J=5.7 Hz, 2 H), 3.48 (q, J=7.0 Hz, 1 H), 3.66 (q, J=5.7 Hz, 2 H), 4.11 (q, J=7.2 Hz, 2 H), 4.30 - 4.54 (m, 2 H), 5.08 (s, 2 H), 6.57 - 6.62 (m, 3 H), 6.82 - 7.02 (m, 2 H), 7.18 - 7.60 (m, 8 H).

[1494]

(2)3-[{[4-({[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]-propanoic acid

Ethyl 3-({[4-({[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}amino)propanoate (0.78 g) synthesized in the above-mentioned (1) was dissolved in ethanol (5 mL), 1N aqueous sodium hydroxide solution (3.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (3.0 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethanol-water to give the title object compound (0.70 g, 94%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.81 - 2.10 (m, 12 H), 2.17 (s, 3 H), 2.50 (br. s., 2H), 3.55 (br. s., 2 H), 4.32 (br. s., 1 H), 5.04 (s, 2 H), 6.51 (d, J=8.7 Hz, 2 H), 6.68 (br. s., 1 H), 6.81 - 6.99 (m, 2 H), 7.23 - 7.59 (m, 8 H).

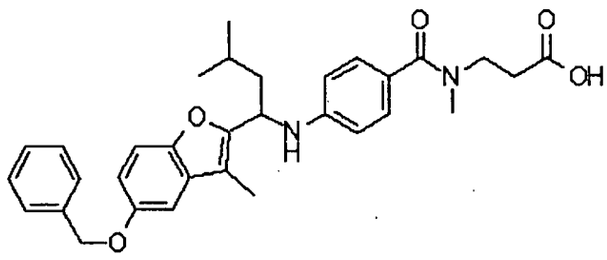
[1495]

Example A159

3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-3-methylbutyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1496]

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[1497]

(1) ethyl 5-(benzyloxy)-3-methyl-1-benzofuran-2-carboxylate

To a solution (200 mL) of 1-[5-(benzyloxy)-2-hydroxyphenyl]ethanone (15.3 g) synthesized in Example A82(1) in N,N-dimethylformamide were added potassium carbonate (13.1 g) and ethyl bromoacetate (7.7 mL) at room temperature, and the mixture was stirred at room temperature for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure, the obtained residue was dissolved in N,N-dimethylformamide (100 mL) again, and 1,8-diazabicyclo[5.4.0]undec-7-ene (12.2 mL) was added to the solution. The reaction mixture was stirred at 80°C overnight. After cooling to room temperature, water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure and the obtained solid was washed with ethanol-isopropyl ether to give the title object compound (3.3 g, 17%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.44 (t, J=7.2 Hz, 3 H), 2.55 (s, 3 H), 4.45 (q, J=7.2 Hz, 2 H), 5.12 (s, 2 H), 7.01 - 7.21 (m, 2 H), 7.30 - 7.60 (m, 6 H).

[1498]

(2) [5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]methanol

To a solution (50 mL) of ethyl 5-(benzyloxy)-3-methyl-1-benzofuran-2-carboxylate (3.3 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added lithium aluminum hydride (0.42 g) under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1

hr then ice-cooled again. water (1.1 mL), 1N aqueous sodium hydroxide solution (5.5 mL), and water (1.1 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give the title object compound (2.8 g, quantitative) as a pale-yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.70 - 1.90 (br. s., 1 H), 2.22 (s, 3 H), 4.73 (d, J=6.0 Hz, 2 H), 5.10 (s, 2 H), 6.88 - 7.06 (m, 2 H), 7.28 - 7.56 (m, 6 H).

[1499]

(3)5-(benzyloxy)-3-methyl-1-benzofuran-2-carbaldehyde

To a solution (30 mL) of [5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]methanol (2.8 g) synthesized in the above-mentioned (2) in toluene was added manganese dioxide (5 g), and the mixture was heated under reflux with a Dean-Stark trap for 1 hr. The reaction mixture was allowed to cool to room temperature, catalyst was filtered through celite. The filtrate was concentrated under reduced pressure to give the title object compound (2.68 g, 94%) as a colorless solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.58 (s, 3 H), 5.12 (s, 2 H), 7.06 - 7.25 (m, 2 H), 7.32 - 7.57 (m, 6 H), 10.00 (s, 1 H).

[1500]

(4) ethyl 3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-3-methylbutyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

To a solution (15 mL) of 5-(benzyloxy)-3-methyl-1-benzofuran-2-carbaldehyde (1.2 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added dropwise isobutylmagnesium bromide (1M, tetrahydrofuran solution) under ice-cooling. The ice bath was removed, the reaction mixture was stirred at room temperature for 15 min, and aqueous ammonium chloride solution was added to quench the reaction. The reaction mixture was extracted with ethyl acetate, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give 1-[5-

(benzyloxy)-3-methyl-1-benzofuran-2-yl]-3-methylbutan-1-ol (0.82 g, 56%) as a pale-yellow oil. This was dissolved in tetrahydrofuran (15 mL), and thionyl chloride (0.35 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (15 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (15 mL), sodium iodide (0.56 g), sodium carbonate (0.38 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.63 g) synthesized in Example 2(2) were added to the solution, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (0.46 g, 33%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.76 - 1.05 (m, 6 H), 1.11 - 1.90 (m, 6 H), 2.24 (s, 3 H), 2.47 - 2.69 (m, 2 H), 3.01 (s, 3 H), 3.56 - 3.80 (m, 2 H), 3.95 - 4.32 (m, 3 H), 4.56 - 4.78 (m, 1 H), 5.09 (s, 2 H), 6.57 (d, J=8.7 Hz, 2 H), 6.80 - 7.02 (m, 2 H), 7.12 - 7.53 (m, 8 H).

[1501]

(5)3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-3-methylbutyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

Ethyl 3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-3-methylbutyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.46 g) synthesized in the above-mentioned (4) was dissolved in ethanol (5 mL), 1N aqueous sodium hydroxide solution (1.5

mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (1.5 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethanol-water to give the title object compound (0.45 g, quantitative) as a colorless solid.

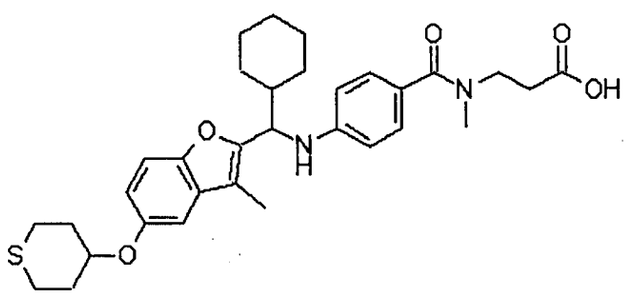
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 (d, 3 H, J=6.0 Hz), 0.99 (d, 3 H, J=6.0 Hz), 1.25 - 2.00 (m, 4 H), 2.24 (s, 3 H), 2.67 (br. s., 2 H), 3.03 (s, 3 H), 3.71 (br. s., 2 H), 4.20 - 4.40 (m, 2 H), 5.08 (s, 2 H), 6.59 - 7.05 (m, 4 H), 7.31 - 7.57 (m, 8 H).

[1502]

Example A160

3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-thiopyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1503]



[1504]

(1) ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-thiopyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

Ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.50 g) synthesized in Example A155(1) was dissolved in tetrahydrofuran (10 mL), and tetrahydrothiopyran-4-ol (142 mg),

tributylphosphine (0.45 mL) and 1,1'-(azodicarbonyl)dipiperidine (0.45 g) were added to the solution under ice-cooling. The ice bath was removed, the reaction mixture was stirred at room temperature for 12 hr, then hexane (10 mL) was added to the mixture, and the precipitate was filtered off through celite. Water was added to the filtrate, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.14 g, 23%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 0.91 - 2.14 (m, 18 H), 2.20 (s, 3 H), 2.46 - 2.99 (m, 6 H), 3.01 (s, 3 H), 3.33 - 3.49 (m, 1 H), 3.70 (t, J=7.1 Hz, 2 H), 4.12 (q, J=7.2 Hz, 2 H), 4.25 - 4.40 (m, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.78 - 6.94 (m, 2 H), 7.16 - 7.30 (m, 3 H).

[1505]

(2)3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-thiopyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

Ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydro-2H-thiopyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.14 g) synthesized in the above-mentioned (1) was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (1.0 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=3:1, volume ratio) to give the title object compound (0.06 g, 46%) as a colorless solid.

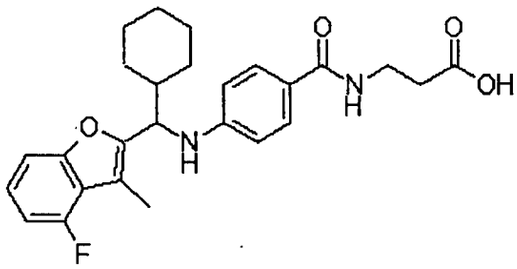
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 - 2.15 (m, 16 H), 2.21 (s, 3 H), 2.41 - 2.95 (m, 6 H), 3.06 (s, 3 H), 3.72 (t, J=6.4 Hz, 2 H), 4.21 - 4.46 (m, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.76 - 6.95 (m, 2 H), 7.22 - 7.26 (m, 3 H).

[1506]

Example A161

3-{[(4-{[cyclohexyl(4-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1507]



[1508]

(1)cyclohexyl(4-fluoro-3-methyl-1-benzofuran-2-yl)methanone

To a solution (50 mL) of 1-(2-fluoro-6-hydroxyphenyl)ethanone (2.5 g) in N,N-dimethylformamide were added potassium carbonate (6.7 g) and 2-bromo-1-cyclohexylethanone (4.0 g) synthesized in Example A51(1) at room temperature, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was allowed to cool to room temperature and filtered through celite. Water was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The obtained residue was dissolved in N,N-dimethylformamide (50 mL) again, 1,8-diazabicyclo[5.4.0]undec-7-ene (2.6 m) was added to the solution, and the mixture was stirred at 110°C for 1 hr with heating. After cooling to room temperature, the reaction mixture was quenched with 1N hydrochloric acid, and the reaction mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure, and the precipitated compound was recrystallized

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from diisopropyl ether-hexane to give the title object compound (2.6 g, 62%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.20 - 2.07 (m, 10 H), 2.73 (s, 3 H), 3.20 - 3.36 (m, 1 H), 6.92 (ddd, J=10.0, 7.8, 0.8 Hz, 1 H), 7.27 - 7.44 (m, 2 H).

[1509]

(2)cyclohexyl(4-fluoro-3-methyl-1-benzofuran-2-yl)methanol

Cyclohexyl(4-fluoro-3-methyl-1-benzofuran-2-yl)methanone (2.6 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (40 mL) and methanol (4 mL), and sodium borohydride (90%, 0.83 g) was added to the solution under ice-cooling. The ice bath was removed, the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (5 mL) and 1N hydrochloric acid (10 mL) were carefully added to the mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (2.5 g, quantitative) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.72 - 2.22 (m, 12 H), 2.35 (s, 3 H), 4.50 (dd, J=8.6, 6.1 Hz, 1 H), 6.86 (ddd, J=10.1, 7.6, 1.3 Hz, 1 H), 7.11 - 7.24 (m, 2 H).

[1510]

(3)3-{[(4-{[cyclohexyl(4-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

Cyclohexyl(4-fluoro-3-methyl-1-benzofuran-2-yl)methanol (0.52 g) synthesized in the above-mentioned (2) was dissolved in tetrahydrofuran (10 mL), and thionyl chloride (0.27 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (5 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was

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extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (10 mL), sodium iodide (0.45 g), sodium carbonate (0.30 g) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.45 g) synthesized in Example 1(2) were added to the solution, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-{[(4-{[cyclohexyl(4-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate (0.12 g, 13%) as a yellow oil. The obtained oil was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.11 g, 95%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 - 2.18 (m, 12 H), 2.37 (s, 3 H), 2.54 (t, J=5.6 Hz, 2 H), 3.41 - 3.75 (m, 2 H), 4.35 (d, J=8.1 Hz, 1 H), 6.44 - 6.64 (m, 3 H), 6.72 - 6.89 (m, 1 H), 7.02 - 7.19 (m, 2 H), 7.52 (d, J=8.5 Hz, 2 H).

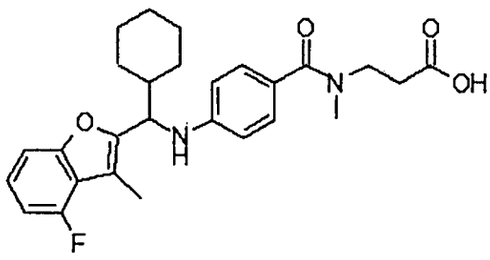
[1511]

Example A162

3-{[(4-{[cyclohexyl(4-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1512]

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[1513]

Cyclohexyl(4-fluoro-3-methyl-1-benzofuran-2-yl)methanol (520 mg) synthesized in Example A161(2) was dissolved in tetrahydrofuran (10 mL), and thionyl chloride (0.27 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (10 mL) was carefully added to the mixture. The mixture was stirred for 10 min, and extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (10 mL), sodium iodide (0.45 g), sodium carbonate (0.30 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.50 g) synthesized in Example 2(2) were added to the solution, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-{[(4-{[cyclohexyl(4-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.15 g, 15%) as a yellow oil. The obtained oil was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed

with water to give the title object compound (0.14 g, 95%) as a colorless solid.

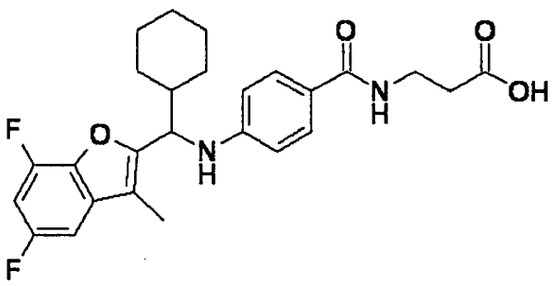
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.88 - 2.16 (m, 12 H), 2.38 (s, 3 H), 2.65 (t, J=6.4 Hz, 2 H), 3.03 (s, 3 H), 3.69 (t, J=6.4 Hz, 2 H), 4.35 (d, J=8.3 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.75 - 6.91 (m, 1 H), 7.03 - 7.18 (m, 2 H), 7.23 (d, J=8.7 Hz, 2 H).

[1514]

Example A163

3-{[(4-{[cyclohexyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1515]



(1)cyclohexyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methanone

To a solution (50 mL) of 1-(3,5-difluoro-2-hydroxyphenyl)ethanone (2.8 g) in N,N-dimethylformamide were added potassium carbonate (6.7 g) and 2-bromo-1-cyclohexylethanone (4.0 g) synthesized in Example A51(1) at room temperature, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was allowed to cool to room temperature, and filtered through celite. Water was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The obtained residue was dissolved in N,N-dimethylformamide (50 mL) again, 1,8-diazabicyclo[5.4.0]undec-7-ene (2.6 mL) was added to the solution, and the mixture was stirred at 110°C 1 hr with heating. After cooling to room temperature, the reaction mixture was quenched with 1N

hydrochloric acid, and the reaction mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure, and the precipitated compound was recrystallized from diisopropyl ether-hexane to give the title object compound (3.1 g, 70%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.09 - 2.09 (m, 10 H), 2.56 (s, 3 H), 3.17 - 3.47 (m, 1 H), 6.93 - 7.16 (m, 2 H).

[1516]

(2)cyclohexyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methanol

Cyclohexyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methanone (3.1 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (50 mL) and methanol (5 mL), and sodium borohydride (90%, 0.93 g) was added to the solution under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (5 mL) and 1N hydrochloric acid (10 mL) were carefully added to the mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (3.1 g, quantitative) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.83 - 2.00 (m, 12 H), 2.20 (s, 3 H), 4.52 (dd, J=8.5, 6.8 Hz, 1 H), 6.79 - 6.93 (m, 2 H).

[1517]

(3)3-{[(4-{[cyclohexyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

Cyclohexyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methanol (0.56 g) synthesized in the above-mentioned (2) was dissolved in tetrahydrofuran (10 mL), and thionyl chloride (0.26 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (10 mL) was carefully added to the mixture.

The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (10 mL), sodium iodide (0.45 g), sodium carbonate (0.30 g) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.45 g) synthesized in Example 1(2) were added to the solution, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-{[(4-{[cyclohexyl(4-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.17 g, 17%) as a yellow oil. The obtained oil was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.16 g, 95%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.87 - 2.14 (m, 12 H), 2.21 (s, 3 H), 2.61 (t, J=5.7 Hz, 2 H), 3.63 (q, J=5.7 Hz, 2 H), 4.39 (d, J=8.3 Hz, 1 H), 6.45 - 6.64 (m, 3 H), 6.67 - 6.81 (m, 1 H), 6.87 (dd, J=8.3, 2.3 Hz, 1 H), 7.53 (d, J=8.7 Hz, 2 H).

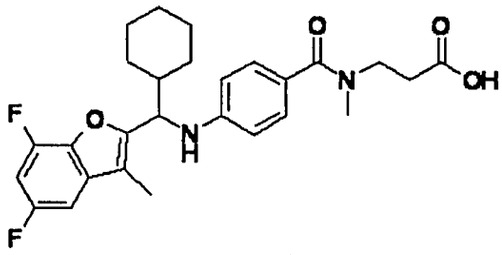
[1518]

Example A164

3-{[(4-{[cyclohexyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1519]

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[1520]

Cyclohexyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methanol (0.56 g) synthesized in Example A163(2) was dissolved in tetrahydrofuran (10 mL), and thionyl chloride (0.26 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (10 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (10 mL), sodium iodide (0.45 g), sodium carbonate (0.30 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.50 g) synthesized in Example 2(2) were added to the solution, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-{[(4-{[cyclohexyl(4-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.17 g, 17%) as a yellow oil. The obtained oil was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid

(1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.15 g, 93%) as a colorless solid.

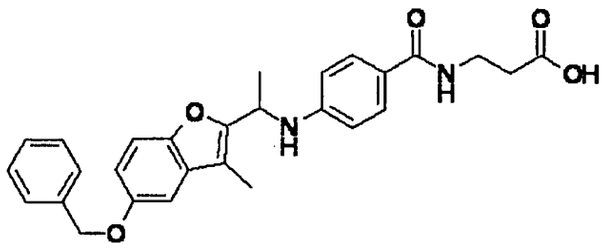
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.88 - 2.16 (m, 12 H), 2.21 (s, 3 H), 2.67 (t, J=6.4 Hz, 2 H), 3.04 (s, 3 H), 3.70 (t, J=6.4 Hz, 2 H), 4.38 (d, J=8.1 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.75 - 6.88 (m, 2 H), 7.23 (d, J=8.7 Hz, 2 H).

[1521]

Example A165

3-({[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]ethyl}amino)phenyl]carbonyl}amino)propanoic acid

[1522]



[1523]

(1)1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]ethanone

To a solution (120 mL) of 1-[5-(benzyloxy)-2-hydroxyphenyl]ethanone (6.4 g) synthesized in Example A82(1) in N,N-dimethylformamide were added potassium carbonate (10.8 g) and bromoacetone (4.8 g) at room temperature, and the mixture was stirred at 80°C for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure, and the obtained residue was dissolved in N,N-dimethylformamide (120 mL) again, and 1,8-diazabicyclo[5.4.0]undec-7-ene (5.1 mL) was added to the solution. The reaction mixture was stirred at 80°C for 2 hr. After cooling to room temperature, water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure, and the obtained solid was washed with ethanol-isopropyl ether

to give the title object compound (2.5 g, 34%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.56 (s, 3 H), 2.60 (s, 3 H), 5.12 (s, 2 H), 7.11 (d, J=2.3 Hz, 1 H), 7.17 (dd, J=8.9, 2.3 Hz, 1 H), 7.30 - 7.55 (m, 6H).

[1524]

(2)1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]ethanol

1-[5-(Benzyloxy)-3-methyl-1-benzofuran-2-yl]ethanone (0.53 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (10 mL) and methanol (1 mL), and sodium borohydride (90%, 0.16 g) was added to the solution under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (1 mL) and 1N hydrochloric acid (5 mL) were carefully added to the mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a crude product (0.53 g, quantitative) of the title object compound as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.62 (d, J=6.6 Hz, 3 H), 1.91 (br. s., 1 H), 2.21 (s, 3 H), 4.95 - 5.21 (m, 3 H), 6.87 - 7.07 (m, 2 H), 7.28 - 7.58 (m, 6 H).

[1525]

(3)3-({[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]ethyl}amino)phenyl]carbonyl}amino)propanoic acid

1-[5-(Benzyloxy)-3-methyl-1-benzofuran-2-yl]ethanol (0.27 g) synthesized in the above-mentioned (2) was dissolved in tetrahydrofuran (5 mL), and thionyl chloride (0.13 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (10 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with

saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (10 mL), sodium iodide (0.21 g), sodium carbonate (0.14 g) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.23 g) synthesized in Example 1(2) were added to the solution, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-({[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]ethyl}amino)phenyl]carbonyl}amino)propanoate (0.15 g, 31%) as a yellow oil. The obtained oil was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.13 g, 88%) as a colorless solid.

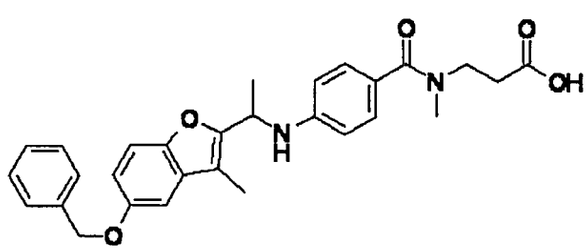
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.62 (d, J=7.0 Hz, 3 H), 2.22 (s, 3 H), 2.69 (d, J=5.7 Hz, 2 H), 3.57 - 3.76 (m, 2 H), 4.65 - 4.88 (m, 1 H), 5.08 (s, 2 H), 6.59 - 6.75 (m, 3 H), 6.82 - 7.04 (m, 2 H), 7.29 - 7.62 (m, 8 H).

[1526]

Example A166

3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]ethyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1527]



[1528]

1-[5-(Benzyloxy)-3-methyl-1-benzofuran-2-yl]ethanol (0.27 g) synthesized in Example A165(2) was dissolved in tetrahydrofuran (5 mL), and thionyl chloride (0.13 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (5 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (10 mL), sodium iodide (0.21 g), sodium carbonate (0.14 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.24 g) synthesized in Example 2(2) were added to the solution, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-{[(4-{[cyclohexyl(4-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.10 g, 20%) as a yellow oil. The obtained oil was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.09 g, 90%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.63 (d, J=6.8 Hz, 3 H), 2.21 (s, 3 H), 2.69 (t, J=6.5 Hz, 2 H), 3.05 (s, 3 H), 3.71 (t, J=6.5

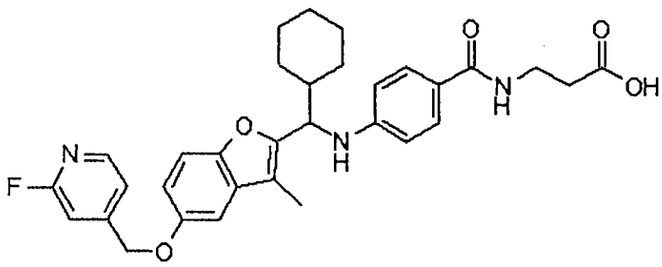
Hz, 2 H), 4.79 (q, J=6.9 Hz, 1 H), 5.09 (s, 2 H), 6.60 (d, J=8.3 Hz, 2 H), 6.84 - 7.02 (m, 2 H), 7.27 - 7.51 (m, 8 H).

[1529]

Example A167

3-[({4-[(cyclohexyl{5-[(2-fluoropyridin-4-yl)methoxy]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[1530]



[1531]

(1) ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate

Ethyl 3-[{[4-({[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}amino]propanoate (5.6 g) synthesized in Example A158(1) was dissolved in ethanol (100 mL), and platinum oxide (0.50 g) was added to the solution. The reaction mixture was stirred under hydrogen atmosphere (1 atm) at room temperature overnight. The reaction mixture was filtered, and the residue was washed with ethanol. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (3.2 g, 68%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 1.94 (m, 14 H), 2.16 (s, 3 H), 2.59 (t, J=5.8 Hz, 2 H), 3.66 (q, J=5.8 Hz, 2 H), 4.03 - 4.14 (m, 2 H), 4.26 - 4.56 (m, 2 H), 5.57 (br. s., 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.61 - 6.68 - 6.71 (m, 1 H), 6.73 (dd, J=8.7, 2.3 Hz, 1 H), 6.83 (d, J=2.3 Hz, 1 H), 7.19 (d, J=8.7 Hz, 1 H), 7.55 (d, J=8.7 Hz, 2 H).

[1532]

683

(2) ethyl 3-[({4-[(cyclohexyl{5-[(2-fluoropyridin-4-yl)methoxy]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoate

Ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate (0.36 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (5 mL), and 2-fluoro-4-pyridinemethanol (114 mg), tributylphosphine (0.35 mL) and 1,1'-(azodicarbonyl)dipiperidine (0.34 g) were added to the solution under ice-cooling. The ice bath was removed, the reaction mixture was stirred at room temperature for 12 hr, then hexane (5 mL) was added to the mixture, and the precipitate was filtered off through celite. Water was added to the filtrate, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.23 g, 54%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 2.00 (m, 14 H), 2.22 (s, 3 H), 2.58 (t, J=5.8 Hz, 2 H), 3.66 (q, J=5.8 Hz, 2 H), 4.15 (q, J=7.0 Hz, 2 H), 4.30 - 4.54 (m, 2 H), 5.13 (s, 2 H), 6.57 - 6.75 (m, 3 H), 6.83 - 6.96 (m, 2 H), 7.05 (s, 1 H), 7.18 - 7.32 (m, 2 H), 7.55 (d, J=8.9 Hz, 2 H), 8.22 (d, J=5.1 Hz, 1 H).

[1533]

(3)3-[({4-[(cyclohexyl{5-[(2-fluoropyridin-4-yl)methoxy]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

Ethyl 3-[({4-[(cyclohexyl{5-[(2-fluoropyridin-4-yl)methoxy]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoate (0.24 g) synthesized in the above-mentioned (2) was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was

evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.17 g, 75%) as a colorless solid.

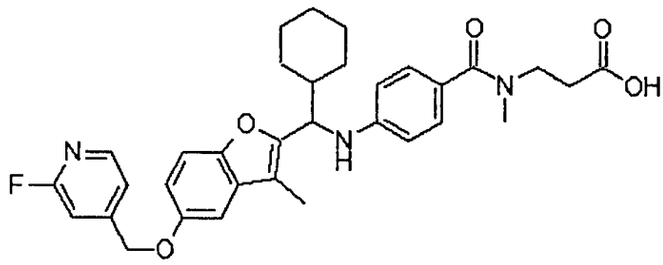
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.83 - 2.13 (m, 12 H), 2.20 (s, 3 H), 2.52 - 2.77 (m, 2 H), 3.52 - 3.77 (m, 2 H), 4.38 (d, J=8.0 Hz, 1 H), 5.14 (s, 2 H), 6.38 - 6.93 (m, 5 H), 7.04 (s, 1 H), 7.17 - 7.25 (m, 2 H), 7.53 (d, J=8.7 Hz, 2 H), 8.21 (d, J=5.3 Hz, 1 H).

[1534]

Example A168

3-[({4-[(cyclohexyl{5-[(2-fluoropyridin-4-yl)methoxy]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

[1535]



[1536]

(1) ethyl 3-[({4-[(cyclohexyl{5-[(2-fluoropyridin-4-yl)methoxy]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate

Ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.35 g) synthesized in Example A155(1) was dissolved in tetrahydrofuran (5 mL), and 2-fluoro-4-pyridinemethanol (108 mg), tributylphosphine (0.32 mL) and 1,1'-(azodicarbonyl)dipiperidine (0.32 g) were added to the solution under ice-cooling. The ice bath was removed, the reaction mixture was stirred at room temperature for 12 hr then hexane (5 mL) was added to the mixture, and the

precipitate was filtered off through celite. Water was added to the filtrate, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.27 g, 62%) as a yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δppm 0.94 - 1.99 (m, 14 H), 2.21 (s, 3 H), 2.61 (br. s., 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.1 Hz, 2 H), 4.12 (q, J=7.0 H z, 2 H), 4.24 - 4.49 (m, 2 H), 5.14 (s, 2 H), 6.56 (d, J=8.5 Hz, 2 H), 6.83 - 6.95 (m, 2 H), 7.06 (s, 1 H), 7.21 - 7.28 (m, 4 H), 8.22 (d, J=5.1 Hz, 1 H).

[1537]

(2)3-[({4-[(cyclohexyl{5-[(2-fluoropyridin-4-yl)methoxy]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid

Ethyl 3-[({4-[(cyclohexyl{5-[(2-fluoropyridin-4-yl)methoxy]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate (0.27 g) synthesized in the above-mentioned (1) was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.21 g, 82%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 - 2.14 (m, 12 H), 2.21 (s, 3 H), 2.67 (t, J=6.4 Hz, 2 H), 3.04 (s, 3 H), 3.70 (t, J=6.4 Hz, 2 H), 4.36 (d, J=8.0 Hz, 1 H), 5.14 (s, 2 H), 6.55 (d, J=8.7 Hz, 2 H), 6.79 - 6.96 (m, 2 H), 7.05 (s, 1 H), 7.20 - 7.35 (m, 4 H), 8.21 (d, J=5.3 Hz, 1 H).

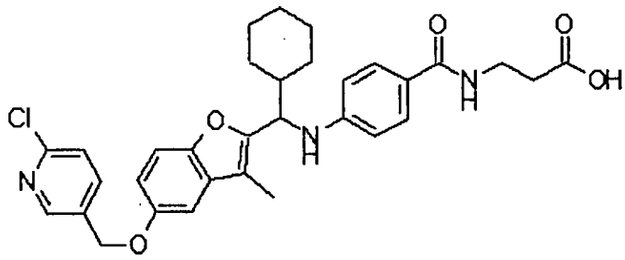
[1538]

Example A169

3-{[(4-{[{5-[(6-chloropyridin-3-yl)methoxy]-3-methyl-1-benzofuran-2-

yl}(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1539]



[1540]

(1) ethyl 3-{[(4-{[{5-[(6-chloropyridin-3-yl)methoxy]-3-methyl-1-benzofuran-2-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoate

Ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate (0.35 g) synthesized in Example A167(1) was dissolved in tetrahydrofuran (5 mL), and 6-chloro-3-pyridinemethanol (0.13 g), tributylphosphine (0.33 mL) and 1,1'-(azodicarbonyl)dipiperidine (0.33 g) were added to the solution under ice-cooling. The ice bath was removed, the reaction mixture was stirred at room temperature for 12 hr then hexane (5 mL) was added to the mixture, and the precipitate was filtered off through celite. Water was added to the filtrate, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.31 g, 65%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 2.13 (m, 14 H), 2.22 (s, 2 H), 2.58 (t, J=5.9 Hz, 2 H), 3.65 (q, J=5.9 Hz, 2 H), 4.25 (q, J=7.0 Hz, 2 H), 4.29 - 4.54 (m, 1 H), 4.71 (d, J=5.3 Hz, 1 H), 5.07 (s, 2 H), 6.48 - 6.68 (m, 3 H), 6.77 - 7.03 (m, 2 H), 7.25 (s, 1 H), 7.24 - 7.40 (m, 2 H), 7.54 (d, J=8.7 Hz, 2 H), 7.68 - 7.76 (m, 1 H), 8.34 - 8.47 (m, 1 H).

[1541]

(2)3-{[(4-{[{5-[(6-chloropyridin-3-yl)methoxy]-3-methyl-1-benzofuran-2-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

Ethyl 3-{[(4-{[{5-[(6-chloropyridin-3-yl)methoxy]-3-methyl-1-benzofuran-2-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl]amino}propanoate (0.31 g) synthesized in the above-mentioned (1) was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.22 g, 74%) as a colorless solid.

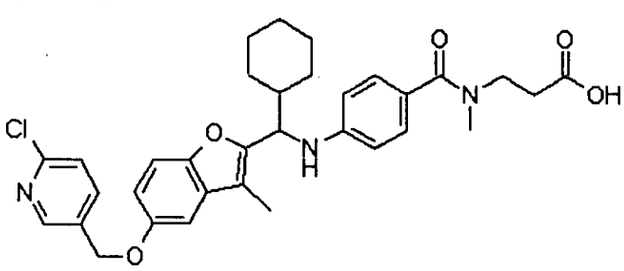
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.88 - 2.13 (m, 12 H), 2.21 (s, 3 H), 2.62 (t, J=5.7 Hz, 2 H), 3.45 - 3.77 (m, 2 H), 4.37 (d, J=8.0 Hz, 1 H), 5.07 (s, 2 H), 6.43 - 6.64 (m, 3 H), 6.75 - 6.99 (m, 2 H), 7.23 - 7.26 (m, 1 H), 7.35 (d, J=8.0 Hz, 1 H), 7.52 (d, J=8.7 Hz, 2 H), 7.76 (dd, J=8.0, 1.9 Hz, 1 H), 8.43 (d, J=1.9 Hz, 1 H).

[1542]

Example A170

3-{[(4-{[{5-[(6-chloropyridin-3-yl)methoxy]-3-methyl-1-benzofuran-2-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[1543]




[1544]

(1) ethyl 3-{[(4-{[{5-[(6-chloropyridin-3-yl)methoxy]-3-methyl-1-benzofuran-2-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate

Ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.39 g) synthesized in Example A155(1) was dissolved in tetrahydrofuran (5 mL), 6-chloro-3-pyridinemethanol (140 mg), tributylphosphine (0.35 mL) and 1,1'-(azodicarbonyl)dipiperidine (0.36 g) were added to the solution under ice-cooling. The ice bath was removed, the reaction mixture was stirred at room temperature for 12 hr then hexane (5 mL) was added to the mixture, and the precipitate was filtered off through celite. Water was added to the filtrate, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.32 g, 66%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.95 - 2.13 (m, 14 H), 2.22 (s, 3H), 2.61 (t, J=5.9 Hz, 2 H), 3.01 (s, 3 H), 3.70 (t, J=5.9 Hz, 2 H), 4.25 (q, J=7.0 Hz, 2 H), 4.29 - 4.71 (m, 2 H), 5.07 (s, 2 H), 6.55 (d, J=8.7 Hz, 2 H), 6.77 - 7.03 (m, 2 H), 7.10 - 7.40 (m, 4 H), 7.68 - 7.76 (m, 1 H), 8.34 - 8.47 (m, 1 H).

[1545]

(2)3-{[(4-{[{5-[(6-chloropyridin-3-yl)methoxy]-3-methyl-1-benzofuran-2-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

Ethyl 3-{[(4-{[{5-[(6-chloropyridin-3-yl)methoxy]-3-methyl-1-benzofuran-2-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (0.32 g) synthesized in the above-mentioned (1) was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide

solution (1.0 mL) was added to the solution at room temperature and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.26 g, 85%) as a colorless solid.

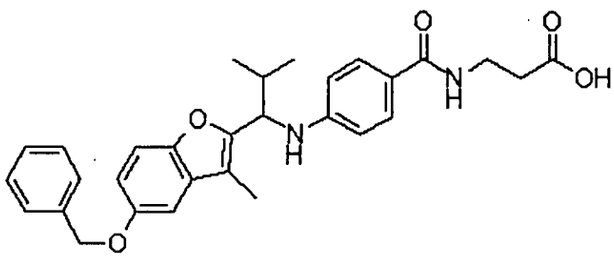
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 - 2.15 (m, 12 H), 2.21 (s, 3 H), 2.52 - 2.77 (m, 2 H), 3.04 (s, 3 H), 3.69 (t, J=6.4 Hz, 2 H), 4.36 (d, J=8.0 Hz, 1 H), 5.08 (s, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.71 - 7.00 (m, 2 H), 7.14 - 7.26 (m, 3 H), 7.36 (d, J=8.0 Hz, 1 H), 7.77 (dd, J=8.0, 1.9 Hz, 1 H), 8.44 (d, J=1.9 Hz, 1 H).

[1546]

Example A171

3-({[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}amino)propanoic acid

[1547]



[1548]

(1) ethyl 3-({[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}amino)propanoate

1-[5-(Benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-ol (1.0 g) synthesized in Example A85(2) was dissolved in tetrahydrofuran (15 mL), and thionyl chloride (0.43 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (15 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with

saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (15 mL), sodium iodide (0.74 g), sodium carbonate (0.50 g) and ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (0.76 g) synthesized in Example 1(2) were added to the solution, and the mixture was stirred at 80°C for 12 hr. After allowed to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (0.43 g, 25%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.4 Hz, 3 H), 1.12 (d, J=7.0 Hz, 3 H), 1.25 (t, J=7.0 Hz, 3 H), 2.16 - 2.34 (m, 4 H), 2.58 (t, J=6.0 Hz, 2 H), 3.66 (q, J=6.0 Hz, 2 H), 4.15 (q, J=7.0 Hz, 2 H), 4.25 - 4.54 (m, 2 H), 5.08 (s, 2 H), 6.48 - 6.66 (m, 3 H), 6.80 - 7.04 (m, 2 H), 7.20 - 7.48 (m, 6 H), 7.55 (d, J=9.0 Hz, 2 H).

[1549]

(2)3-({[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}amino)propanoic acid

Ethyl 3-({[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}amino)propanoate (0.43 g) synthesized in the above-mentioned (1) was dissolved in ethanol (10 mL), 1N aqueous sodium hydroxide solution (2.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (2.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.36 g, 89%) as a colorless solid.

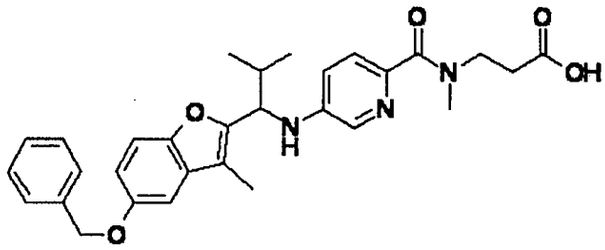
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 (d, J=6.4 Hz, 3 H), 1.13 (d, J=6.4 Hz, 3 H), 2.10 - 2.40 (m, 4 H), 2.67 (br. s., 2 H), 3.66 (br. s., 2 H), 4.35 (br. s., 1 H), 5.08 (s., 2 H), 6.44 - 6.69 (m, 3 H), 6.79 - 7.68 (m, 10 H).

[1550]

Example A172

3-[{[5-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridin-2-yl]carbonyl}(methyl)amino]propanoic acid

[1551]



[1552]

(1) methyl 5-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridine-2-carboxylate

1-[5-(Benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-ol (1.0 g) synthesized in Example A58(2) was dissolved in tetrahydrofuran (15 mL), and thionyl chloride (0.43 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (15 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (15 mL), sodium iodide (0.74 g), sodium carbonate (0.50 g) and methyl 5-aminopyridine-2-carboxylate (0.50 g) were added to the solution, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (0.22 g, 15%) as a

yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 (d, J=6.8 Hz, 3 H), 1.15 (d, J=6.8 Hz, 3 H), 2.16 - 2.40 (m, 4 H), 3.91 (s, 3 H), 4.35 (t, J=8.1 Hz, 1 H), 4.65 (d, J=8.7 Hz, 1 H), 5.08 (s, 2 H), 6.72 - 7.03 (m, 3 H), 7.18 - 7.53 (m, 6 H), 7.89 (d, J=8.3 Hz, 1 H), 8.10 (d, J=2.6 Hz, 1 H).

[1553]

(2) ethyl 3-[{[5-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridin-2-yl]carbonyl}(methyl)amino]propanoate

Methyl 5-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridine-2-carboxylate (0.22 g) synthesized in the above-mentioned (1) was dissolved in ethanol (5 mL), and 1N aqueous sodium hydroxide solution (1 mL) was added to the solution at room temperature. The reaction mixture was stirred at 70°C for 30 min, allowed to cool to room temperature, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (1 mL), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.17 g), 1-hydroxybenzotriazole·monohydrate (0.14 g) and ethyl 3-(methylamino)propanoate (0.10 g) were added to the solution at room temperature, and the mixture was stirred overnight. Water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (0.15 g, 56%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 (d, J=6.4 Hz, 3 H), 1.14 (d, J=6.4 Hz, 3 H), 1.26 (t, J=7.2 Hz, 3 H), 2.16 - 2.36 (m, 4 H), 2.60 - 2.80 (m, 2 H), 3.80 (br. s., 2 H), 4.12 (q, J=7.2 Hz, 2 H), 4.22 - 4.48 (m, 2 H), 5.09 (s, 2 H), 6.79 - 7.05 (m, 3 H), 7.24 - 7.51 (m, 7 H), 7.93 (br. s., 1 H).

[1554]

(3)3-[{[5-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-

methylpropyl}amino)pyridin-2-yl]carbonyl}(methyl)amino]propanoic acid

Ethyl 3-[{[5-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridin-2-yl]carbonyl}(methyl)amino]propanoate (0.15 g) synthesized in the above-mentioned (2) was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.14 g, quantitative) as a colorless solid.

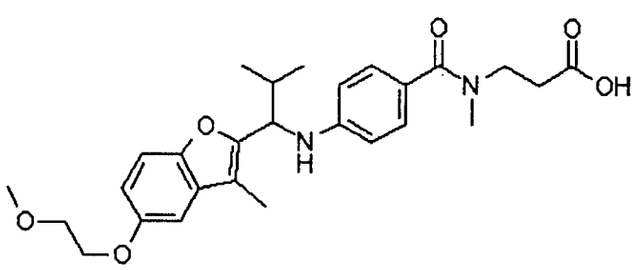
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 (d, J=6.8 Hz, 3 H), 1.15 (d, J=6.8 Hz, 3 H), 2.24 (s, 3 H), 2.27 - 2.39 (m, 1 H), 2.82 (br. s., 2 H), 3.10 (s, 3 H), 3.77 (t, J=6.4 Hz, 2 H), 4.31 (d, J=7.9 Hz, 1 H), 5.09 (s, 2 H), 6.85 - 7.03 (m, 3 H), 7.29 - 7.61 (m, 7 H), 8.04 (br. s., 1 H).

[1555]

Example A173

3-[{[4-({1-[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1556]



[1557]

(1)1-[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-one

To a solution (10 mL) of 1-[2-hydroxy-5-(2-methoxyethoxy)phenyl]ethanone (0.55 g) synthesized in Example

694

A79(1) in N,N-dimethylformamide were added potassium carbonate (1.1 g) and 1-bromo-3-methylbutan-2-one (0.56 g) synthesized in Example A75(1) at room temperature, and the mixture was stirred for 15 hr. The reaction mixture was filtered through celite, water (200 mL) was added and the mixture was extracted with diethyl ether (10 mL×2). The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (10 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.41 mL) was added to the solution at room temperature. The reaction mixture was stirred at 100°C for 1 hr. The reaction mixture was allowed to cool to room temperature, 1N hydrochloric acid (10 mL) was added, and the mixture was extracted with diethyl ether (10 mL×2). The extract was washed with water, saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (0.71 g, 98%) as a pale-yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.23 (d, J=6.8 Hz, 6 H), 2.57 (s, 3 H), 3.48 (s, 3 H), 3.56 (quin, J=6.8 Hz, 1 H), 3.74 - 3.85 (m, 2 H), 4.10 - 4.24 (m, 2 H), 7.05 (d, J=2.6 Hz, 1 H), 7.14 (dd, J=9.0, 2.6 Hz, 1 H), 7.39 (d, J=9.0 Hz, 1 H).

[1558]

(2)1-[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-ol

1-[5-(2-Methoxyethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-one (0.71 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (5 mL) and methanol (0.5 mL), and sodium borohydride (90%, 0.21 g) was added to the solution under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (1 mL) and 1N hydrochloric acid (5 mL) were carefully added to the mixture, and the mixture was

extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a crude product (0.70 g, quantitative) of the title object compound as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.82 (d, J=6.8 Hz, 3 H), 1.12 (d, J=6.8 Hz, 3 H), 1.96 (br. s., 1 H), 2.12 - 2.33 (m, 4 H), 3.47 (s, 3 H), 3.70 - 3.85 (m, 2 H), 4.10 - 4.23 (m, 2 H), 4.46 (d, J=8.3 Hz, 1 H), 6.79 - 7.01 (m, 2 H), 7.30 (d, J=8.7 Hz, 1 H).

[1559]

(3)3-[{[4-({1-[5-(2-methoxyethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

1-[5-(2-Methoxyethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-ol (0.70 g) synthesized in the above-mentioned (2) was dissolved in tetrahydrofuran (10 mL), and thionyl chloride (0.34 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (5 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (10 mL), sodium iodide (0.56 g), sodium carbonate (0.38 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.63 g) synthesized in Example 2(2) were added to the solution and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({1-[5-(2-methoxyethoxy)-3-methyl-

1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.10 g, 8%) as a yellow oil. The obtained oil was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.05 g, 52%) as a colorless solid.

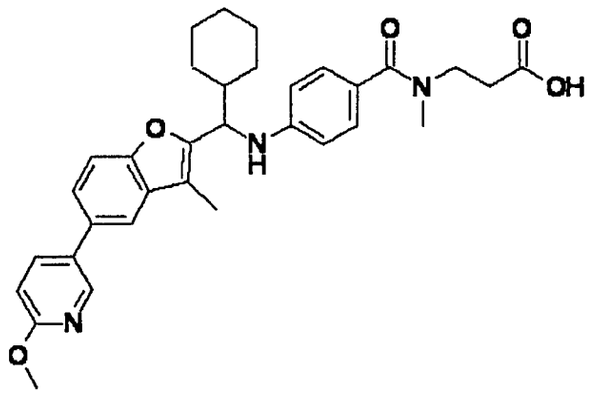
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.4 Hz, 3 H), 1.12 (d, J=6.4 Hz, 3 H), 2.21 (s, 3 H), 2.23 - 2.36 (m, 1 H), 2.67 (t, J=6.4 Hz, 2 H), 3.04 (s, 3 H), 3.46 (s, 3 H), 3.69 (t, J=6.4 Hz, 2 H), 3.73 - 3.84 (m, 2 H), 4.15 (dd, J=5.7, 3.8 Hz, 2 H), 4.32 (d, J=7.5 Hz, 1 H), 6.57 (d, J=8.7 Hz, 2 H), 6.76 - 6.98 (m, 2 H), 7.15 - 7.25 (m, 3 H).

[1560]

Example A174

3-[{[4-({cyclohexyl[5-(6-methoxypyridin-3-yl)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1561]



[1562]

(1)(5-bromo-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methanone

1-[5-Bromo-2-hydroxyphenyl]ethanone (13.4 g) was dissolved in N,N-dimethylformamide (300 mL). To the reaction

mixture were added potassium carbonate (25.8 g) and 2-bromo-1-cyclohexylethanone (19.0 g) synthesized in Example A51(1) at room temperature, and the mixture was stirred for 3 hr. The reaction mixture was filtered through celite, water (200 mL) was added, and the mixture was extracted with diethyl ether (100 mL×2). The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (150 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (9.3 mL) was added to the solution at room temperature, and the mixture was stirred at 100°C for 1 hr. The reaction mixture was allowed to cool to room temperature, 1N hydrochloric acid (70 mL) was added, and the mixture was extracted with diethyl ether (100 mL×2). The extract was washed with water, saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The precipitate was washed with diisopropyl ether to give the title object compound (15.4 g, 77%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.16 - 2.05 (m, 10 H), 2.56 (s, 3 H), 3.20 - 3.36 (m, 1 H), 7.40 (d, J=8.9 Hz, 1 H), 7.55 (dd, J=8.9, 1.5 Hz, 1 H), 7.77 (d, J=1.5 Hz, 1 H).

[1563]

(2) (5-bromo-3-methyl-1-benzofuran-2-yl) (cyclohexyl)methanol

(5-Bromo-3-methyl-1-benzofuran-2-yl) (cyclohexyl)methanone (7.5 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (100 mL) and methanol (15 mL), and sodium borohydride (90%, 1.9 g) was added to the solution under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (10 mL) and 1N hydrochloric acid (50 mL) were carefully added to the mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a crude product (7.4 g, quantitative)

of the title object compound as a pale-yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.83 - 2.11 (m, 11 H), 2.19 (s, 3 H), 3.62 - 3.85 (m, 1 H), 4.51 (br. s., 1 H), 7.27 - 7.59 (m, 3 H).

[1564]

(3) ethyl 3-{[(4-{[(5-bromo-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate

(5-Bromo-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methanol (7.5 g) synthesized in the above-mentioned (2) was dissolved in tetrahydrofuran (150 mL), and thionyl chloride (3.1 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (75 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (100 mL), sodium iodide (5.2 g), sodium carbonate (3.5 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (5.8 g) synthesized in Example 2(2) were added to the solution, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (6.0 g, 47%) as a pale-yellow solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.88 - 1.97 (m, 14 H), 2.22 (s, 3 H), 2.61 (t, J=7.1 Hz, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.1 Hz, 2 H), 3.99 - 4.17 (m, 2 H), 4.23 - 4.47 (m, 2 H), 6.55 (d, J=8.7 Hz, 2 H), 7.11 - 7.37 (m, 4 H), 7.54 (d, J=1.7 Hz, 1 H).

[1565]

(4)3-[{[4-({cyclohexyl[5-(6-methoxypyridin-3-yl)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (5 mL) of ethyl 3-{[(4-{[(5-bromo-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.25 g) synthesized in the above-mentioned (3) in N,N-dimethylacetamide were added (6-methoxypyridin-3-yl)boronic acid (0.14 g), potassium carbonate (0.13 g) and tetrakistriphenylphosphine palladium (0.05 g), and the mixture was stirred at 90°C for 12 hr under nitrogen atmosphere. The reaction mixture was cooled to room temperature, and filtered through celite and the residue was washed with diethyl ether. Water was added to the filtrate, and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[5-(6-methoxypyridin-3-yl)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.15 g, 58%) as a pale-yellow oil. The obtained oil was dissolved in ethanol (1 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.12 g, 85%) as a pale-yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.27 - 2.19 (m, 12 H), 2.29 (s, 3 H), 2.69 (t, J=6.4 Hz, 2 H), 3.05 (s, 3 H), 3.70 (t, J=6.4 Hz, 2 H), 3.99 (s, 3 H), 4.41 (d, J=7.9 Hz, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 6.83 (d, J=9.0 Hz, 1 H), 7.19 - 7.26 (m, 2 H), 7.32 - 7.53 (m, 3 H), 7.81 (dd, J=8.5, 2.4 Hz, 1 H), 8.38 (d, J=2.3 Hz, 1 H).

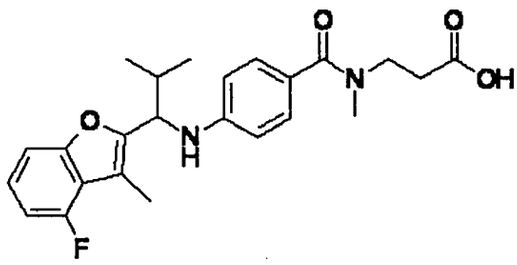
[1566]

Example A175

3-{[(4-{[1-(4-fluoro-3-methyl-1-benzofuran-2-yl)-2-

methylpropyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1567]



[1568]

(1)1-(4-fluoro-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-one

To a solution (25 mL) of 1-(2-fluoro-6-hydroxyphenyl)ethanone (1.3 g) in N,N-dimethylformamide were added potassium carbonate (3.5 g) and 1-bromo-3-methylbutan-2-one (1.7 g) synthesized in Example A75(1) at room temperature, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was allowed to cool to room temperature, and filtered through celite. Water was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The obtained residue was dissolved in N,N-dimethylformamide (15 mL) again, 1,8-diazabicyclo[5.4.0]undec-7-ene (1.3m) was added to the mixture, and the mixture was stirred at 110°C for 1 hr with heating. After cooling to room temperature, the reaction mixture was quenched with 1N hydrochloric acid, and the mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure, and the precipitated compound was recrystallized from diisopropyl ether-hexane to give the title object compound (1.4 g, 77%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.24 (d, J=6.8 Hz, 6 H), 2.74 (s, 3 H), 3.50 - 3.66 (m, 1 H), 6.93 (dd, J=10.2, 7.9 Hz, 1 H), 7.28 - 7.50 (m, 2 H).

[1569]

(2)1-(4-fluoro-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-ol

1-(4-Fluoro-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-one (1.4 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (20 mL) and methanol (2 mL), and sodium borohydride (90%, 0.53 g) was added to the solution under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (2 mL) and 1N hydrochloric acid (5 mL) were carefully added to the mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a crude product (1.4 g, quantitative) of the title object compound as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.82 (d, J=6.8 Hz, 3 H), 1.13 (d, J=6.8 Hz, 3 H), 1.99 (d, J=5.7 Hz, 1 H), 2.22 (dt, J=8.3, 6.8 Hz, 1 H), 2.36 (s, 3 H), 4.46 (dd, J=8.3, 5.7 Hz, 1 H), 6.77 - 7.23 (m, 3 H).

[1570]

(3)3-{[(4-{[1-(4-fluoro-3-methyl-1-benzofuran-2-yl)-2-methylpropyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

1-(4-Fluoro-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-ol (1.4 g) synthesized in the above-mentioned (2) was dissolved in tetrahydrofuran (20 mL), and thionyl chloride (0.84 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (20 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (30 mL), sodium iodide (1.4 g), sodium carbonate (0.96 g) and ethyl 3-{[(4-

aminophenyl)carbonyl](methyl)amino}propanoate (1.6 g) synthesized in Example 2(2) were added to the solution, and the mixture was stirred at 80°C for 12 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-{[(4-{[1-(4-fluoro-3-methyl-1-benzofuran-2-yl)-2-methylpropyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.20 g, 7%) as a yellow oil. The obtained oil was dissolved in ethanol (2 mL), 1N aqueous sodium hydroxide solution (2.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (2.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.06 g, 32%) as a pale-yellow solid.

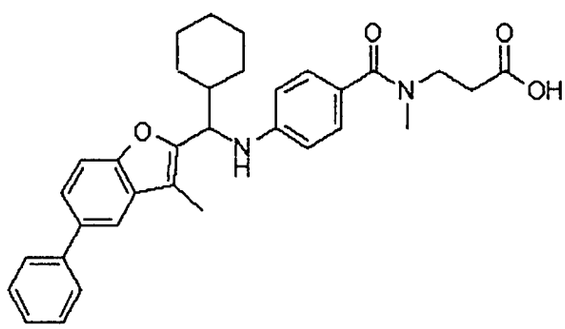
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 (d, J=6.4 Hz, 3 H), 1.14 (d, J=6.4 Hz, 3 H), 2.09 - 2.32 (m, 1 H), 2.39 (s, 3 H), 2.69 (t, J=6.2 Hz, 2 H), 3.05 (s, 3 H), 3.71 (t, J=6.2 Hz, 2 H), 4.31 (d, J=7.9 Hz, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 6.76 - 7.19 (m, 3 H), 7.25 (d, J=8.7 Hz, 2 H).

[1571]

Example A176

3-{[(4-{[cyclohexyl(3-methyl-5-phenyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1572]



[1573]

To a solution (5 mL) of ethyl 3-{[(4-{[(5-bromo-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (0.28 g) synthesized in Example A174(3) in N,N-dimethylacetamide were added phenylboronic acid (0.12 g), potassium carbonate (0.14 g) and tetrakistriphenylphosphine palladium (0.10 g), and the mixture was stirred at 70°C for 12 hr under nitrogen atmosphere. The reaction mixture was cooled to room temperature, and filtered through celite, and the residue was washed with diethyl ether. Water was added to the filtrate, and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-{[(4-{[cyclohexyl(3-methyl-5-phenyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.15 g, 54%) as a pale-yellow oil. The obtained oil was dissolved in ethanol (1 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.09 g, 67%) as a colorless solid.

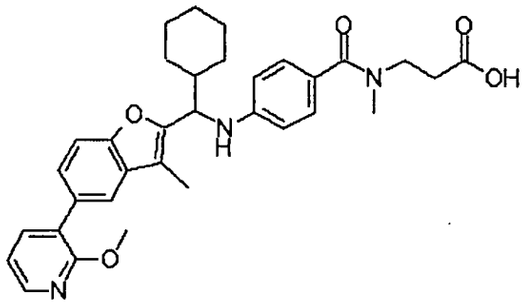
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 - 2.16 (m, 11 H), 2.29 (s, 3 H), 2.69 (t, J=6.2 Hz, 2 H), 3.05 (s, 3 H), 3.72 (t, J=6.2 Hz, 2 H), 4.41 (d, J=7.9 Hz, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 7.23 - 7.66 (m, 10 H).

[1574]

Example A177

3-[{[4-({cyclohexyl[5-(2-methoxypyridin-3-yl)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1575]



[1576]

To a solution (15 mL) of ethyl 3-{[(4-{[(5-bromo-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (0.53 g) synthesized in Example A174(3) in N,N-dimethylacetamide were added (2-methoxypyridin-3-yl)boronic acid (0.29 g), potassium carbonate (0.27 g) and tetrakistriphenylphosphine palladium (0.05 g), and the mixture was stirred at 90°C for 12 hr under nitrogen atmosphere. The reaction mixture was cooled to room temperature and filtered through celite, and the residue was washed with diethyl ether. Water was added to the filtrate, and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[5-(2-methoxypyridin-3-yl)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.50 g, 89%) as a pale-yellow oil. The obtained oil was dissolved in ethanol (1 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.47 g, quantitative) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.97 - 2.15 (m, 11 H), 2.27 (s, 3 H), 2.49 - 2.65 (m, 2 H), 2.99 (s, 3 H), 3.65 (br. s., 2 H), 3.95 (s, 3 H), 4.39 (d, J=7.9 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2

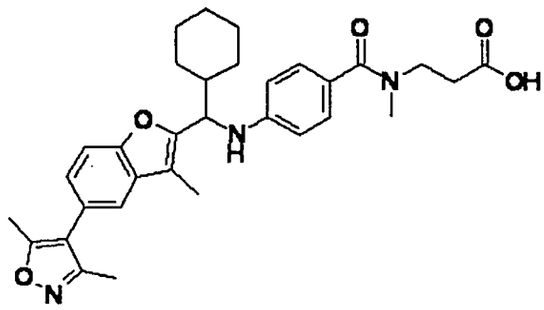
H), 6.97 (dd, J=7.2, 4.9 Hz, 1 H), 7.23 (d, J=8.7 Hz, 2 H), 7.38 - 7.66 (m, 4 H), 8.15 (dd, J=5.1, 2.1 Hz, 1 H).

[1577]

Example A178

3-[{[4-({cyclohexyl[5-(3,5-dimethylisoxazol-4-yl)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1578]



[1579]

To a solution (15 mL) of ethyl 3-{[(4-{[(5-bromo-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (0.54 g) synthesized in Example A174(3) in toluene were added (3,5-dimethylisoxazol-4-yl)boronic acid (0.41 g) and 2N aqueous sodium carbonate solution (1.46 mL), and the mixture was stirred at room temperature for 10 min under argon atmosphere. To the reaction mixture were added 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl(0.05 g) and tris(dibenzylideneacetone)dipalladium (0) (0.03 g), and the mixture was heated under reflux under argon atmosphere overnight. The reaction mixture was cooled to room temperature and filtered through celite, and the residue was washed with diethyl ether. Water was added to the filtrate, and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[5-(3,5-dimethylisoxazol-4-yl)-3-methyl-1-benzofuran-2-

yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.13 g, 23%) as a pale-yellow oil. The obtained oil was dissolved in ethanol (1 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.12 g, 96%) as a colorless solid.

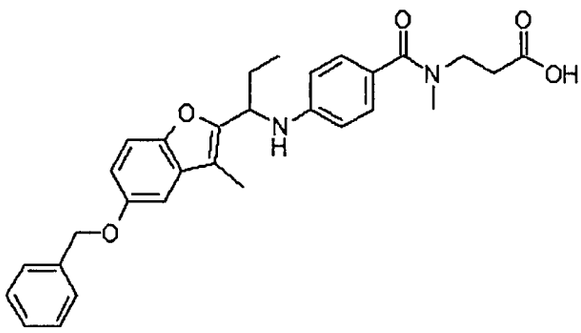
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 2.19 (m, 11 H), 2.26 (s, 3 H), 2.27 (s, 3 H), 2.39 (s, 3 H), 2.71 (t, J=6.2 Hz, 2 H), 3.07 (s, 3 H), 3.73 (t, J=6.2 Hz, 2 H), 4.41 (d, J=7.9 Hz, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 7.08 (dd, J=8.3, 1.5 Hz, 1 H), 7.20 - 7.26 (m, 3 H), 7.42 (d, J=8.3 Hz, 1 H).

[1580]

Example A179

3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]propyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1581]



[1582]

(1)1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]propan-1-one

To a solution (150 mL) of 1-[5-(benzyloxy)-2-hydroxyphenyl]ethanone (7.8 g) synthesized in Example 82(1) in N,N-dimethylformamide were added potassium carbonate (13.2 g) and 1-bromobutan-2-one (5.0 mL) at room temperature, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was allowed to cool to room temperature, and filtered

through celite. Water was added to the filtrate, and the mixture was extracted with diethyl ether. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The obtained residue was dissolved in N,N-dimethylformamide (100 mL) again, 1,8-diazabicyclo[5.4.0]undec-7-ene (4.9 mL) was added to the solution, and the mixture was stirred at 110°C with heating for 1 hr. After cooling to room temperature, the reaction mixture was quenched with 1N hydrochloric acid, and the mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure, and the precipitated compound was recrystallized from diisopropyl ether-hexane to give the title object compound (6.2 g, 66%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.22 (t, J=7.2 Hz, 3 H), 2.57 (s, 3 H), 3.01 (q, J=7.2 Hz, 2 H), 5.12 (s, 2 H), 7.04 - 7.52 (m, 8 H).

[1583]

(2)1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]propan-1-ol

1-[5-(Benzyloxy)-3-methyl-1-benzofuran-2-yl]propan-1-one (0.88 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (15 mL)and methanol (1 mL), and sodium borohydride (90%, 0.25 g) was added to the solution under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (2 mL) and 1N hydrochloric acid (5 mL) were carefully added to the mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a crude product (0.85 g, quantitative) of the title object compound as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 (t, J=7.4 Hz, 3 H), 1.92 - 2.03 (m, 3 H), 2.21 (s, 3 H), 4.69 - 4.87 (m, 1 H), 5.11 (s, 2 H), 6.89 - 7.51 (m, 8 H).

[1584]

(3)3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]propyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

1-[5-(Benzyloxy)-3-methyl-1-benzofuran-2-yl]propan-1-ol (0.85 g) synthesized in the above-mentioned (2) was dissolved in tetrahydrofuran (15 mL), and thionyl chloride (0.40 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (20 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (15 mL), sodium iodide (0.67 g), sodium carbonate (0.45 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.75 g) synthesized in Example 2(2) were added to the solution and the mixture was stirred at 80°C for 4 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]propyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.15 g, 9%) as a yellow oil. The obtained oil was dissolved in ethanol (2 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.10 g, 71%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 (t, J=7.3 Hz, 3 H), 1.87 - 2.08 (m, 2 H), 2.23 (s, 3 H), 2.66 (t, J=6.2 Hz, 2 H), 3.03 (s,

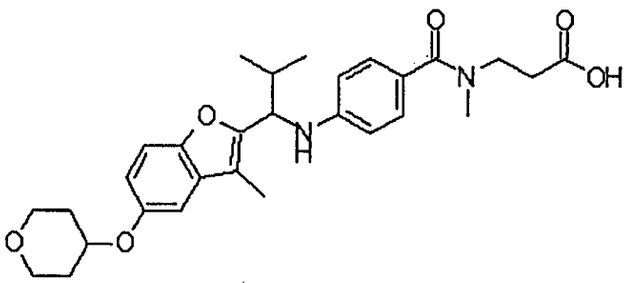
3 H), 3.70 (t, J=6.2 Hz, 2 H), 4.52 (dd, J=8.3, 6.2 Hz, 1 H), 5.09 (s, 2 H), 6.57 (d, J=8.7 Hz, 2 H), 6.82 - 7.02 (m, 2 H), 7.18 - 7.51 (m, 8 H).

[1585]

Example A180

3-(methyl{[4-({2-methyl-1-[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]propyl}amino)phenyl]carbonyl}amino)propanoic acid

[1586]



[1587]

(1)1-(5-hydroxy-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-one

To a solution of 1-[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-one (11.4 g) synthesized in Example A85(1) in ethanol (200 mL) was added palladium carbon-ethylenediamine complex (1.1 g) at room temperature. The reaction mixture was stirred under hydrogen atmosphere (1 atm) at room temperature for 16 hr, and the catalyst was filtered off. The filtrate was concentrated under reduced pressure to give a crude product (8.0 g, quantitative) of the title object compound as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.24 (d, J=6.8 Hz, 6 H), 2.55 (s, 3 H), 3.48 - 3.63 (m, 1 H), 6.95 - 7.40 (m, 3 H).

[1588]

(2)3-(methyl{[4-({2-methyl-1-[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]propyl}amino)phenyl]carbonyl}amino)propanoic acid

1-(5-Hydroxy-3-methyl-1-benzofuran-2-yl)-2-methylpropan-

1-one (1.1 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (15 mL) and methanol (1 mL), and sodium borohydride (90%, 0.30 g) was added to the solution under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (5 mL) and 1N hydrochloric acid (15 mL) were carefully added to the mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give 1-(5-hydroxy-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-ol (0.71 g, 65%) as a pale-yellow oil. The obtained oil was dissolved in tetrahydrofuran (15 mL), and thionyl chloride (0.30 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (20 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (15 mL), sodium iodide (0.52 g), sodium carbonate (0.35 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.58 g) synthesized in Example 2(2) were added to the mixture, and the mixture was stirred at 70°C for 4 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-(methyl{[4-({2-methyl-1-[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]propyl}amino)phenyl]carbonyl}amino)propanoate (0.54 g, 46%) as a yellow oil. The obtained oil was dissolved in ethanol (3 mL), 1N aqueous sodium hydroxide solution (3.0 mL) was added

to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (3.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.53 g, 98%) as a colorless solid.

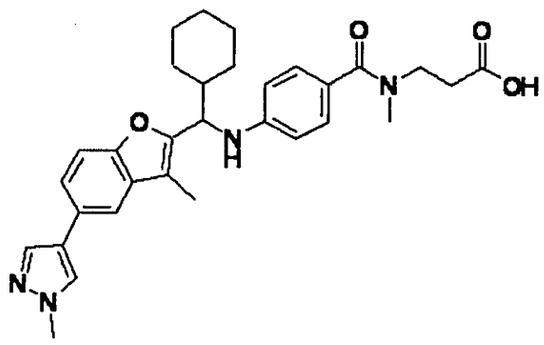
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 (d, J=6.8 Hz, 3 H), 1.13 (d, J=6.8 Hz, 3 H), 1.70 - 2.09 (m, 4 H), 2.21 (s, 3 H), 2.22 - 2.27 (m, 1 H), 2.67 (t, J=6.2 Hz, 2 H), 3.04 (s, 3 H), 3.56 (ddd, J=11.5, 8.5, 3.4 Hz, 2 H), 3.70 (t, J=6.2 Hz, 2 H), 3.91 - 4.08 (m, 2 H), 4.32 (d, J=7.6 Hz, 1 H), 4.43 (tt, J=7.9, 3.8 Hz, 1 H), 6.57 (d, J=8.7 Hz, 2 H), 6.85 (dd, J=8.7, 2.7 Hz, 1 H), 6.93 (d, J=2.3 Hz, 1 H), 7.19 - 7.26 (m, 3 H).

[1589]

Example A181

3-[{[4-({cyclohexyl[3-methyl-5-(1-methyl-1H-pyrazol-4-yl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1590]



[1591]

To a solution (15 mL) of ethyl 3-{[(4-{[(5-bromo-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (0.59 g) synthesized in Example A174(3) in N,N-dimethylacetamide were added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.44 g), potassium carbonate (0.29 g) and tetrakistriphenylphosphine palladium (0.06 g), and the mixture was stirred at 70°C for 24 hr under

argon atmosphere. The reaction mixture was cooled to room temperature, and filtered through celite, and the residue was washed with diethyl ether. Water was added to the filtrate, and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(1-methyl-1H-pyrazol-4-yl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.23 g, 39%) as a pale-yellow oil. The obtained oil was dissolved in ethanol (1 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.04 g, 16%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 2.11 (m, 11 H), 2.27 (s, 3 H), 2.67 (br. s., 2 H), 3.03 (s, 3 H), 3.70 (t, J=6.2 Hz, 2 H), 3.94 (s, 3 H), 4.38 (d, J=7.8 Hz, 1 H), 6.57 (d, J=8.6 Hz, 2 H), 7.23 (d, J=8.6 Hz, 2 H), 7.29 - 7.39 (m, 2 H), 7.49 (s, 1 H), 7.59 (s, 1 H), 7.75 (s, 1 H).

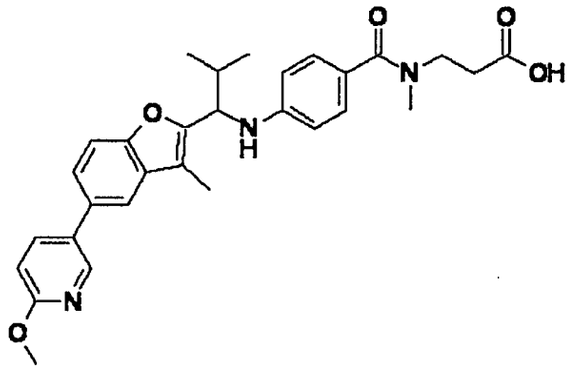
[1592]

Example A182

3-[{[4-({1-[5-(6-methoxypyridin-3-yl)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1593]

713



[1594]

(1) 1-(5-bromo-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-one

1-[5-Bromo-2-hydroxyphenyl]ethanone (8.4 g) was dissolved in N,N-dimethylformamide (50 mL). To the reaction mixture were added carbonate (16.2 g) and 1-bromo-3-methylbutan-2-one (8.4 g) synthesized in Example A75(1) at room temperature potassium, and the mixture was stirred at 60°C for 1 hr. The reaction mixture was filtered through celite, water (100 mL) was added, and the mixture was extracted with diethyl ether (50 mL×2). The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The precipitate was washed with diisopropyl ether to give the title object compound (10.2 g, 77%) as a pale-yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.25 (d, J=6.8 Hz, 6 H), 2.57 (s, 3 H), 3.48 - 3.70 (m. 1 H), 7.39 (d, J=8.7 Hz, 1 H), 7.55 (dd, J=8.7, 1.9 Hz, 1 H), 7.78 (d, J=1.9 Hz, 1 H).

[1595]

(2) ethyl 3-{[(4-{[1-(5-bromo-3-methyl-1-benzofuran-2-yl)-2-methylpropyl]amino}phenyl)carbonyl](methyl)amino}propanoate

1-(5-Bromo-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-one (6.2 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (100 mL) and methanol (10 mL), and sodium borohydride (90%, 1.8 g) was added to the solution under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (10 mL) and 1N hydrochloric acid (50 mL) were carefully added to the mixture, and the mixture was

extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give 1-(5-bromo-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-ol (6.1 g, quantitative) as a pale-yellow oil. The obtained oil was dissolved in tetrahydrofuran (50 mL), and thionyl chloride (2.3 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (30 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (100 mL), sodium iodide (3.9 g), sodium carbonate (2.7 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (4.4 g) synthesized in Example 2(2) were added to the solution, and the mixture was stirred at 70°C for 4 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (1.12 g, 12%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.4 Hz, 3 H), 1.13 (d, J=6.4 Hz, 3 H), 1.18 - 1.26 (t, J=7.2 Hz, 3 H), 2.20 - 2.35 (m, 4 H), 2.61 (t, J=7.0 Hz, 2 H), 3.01 (s, 4 H), 3.70 (t, J=7.0 Hz, 2 H), 4.09 - 4.17 (m, 2 H), 4.24 - 4.41 (m, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 7.15 - 7.36 (m, 4 H), 7.55 (d, J=1.9 Hz, 1 H).

[1596]

(3)3-[{[4-({1-[5-(6-methoxypyridin-3-yl)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (10 mL) of ethyl 3-{[(4-{[1-(5-bromo-3-methyl-1-benzofuran-2-yl)-2-methylpropyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.55 g) synthesized in the above-mentioned (2) in N,N-dimethylacetamide were added (6-methoxypyridin-3-yl)boronic acid (0.33 g), potassium carbonate (0.29 g) and tetrakistriphenylphosphine palladium (0.12 g), and the mixture was stirred at 70°C for 24 hr under argon atmosphere. The reaction mixture was cooled to room temperature, and filtered through celite, and the residue was washed with diethyl ether. Water was added to the filtrate, and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({1-[5-(6-methoxypyridin-3-yl)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.10 g) as a pale-yellow oil. The obtained oil was dissolved in ethanol (1 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.06 g, 10%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 (d, J=6.8 Hz, 3 H), 1.15 (d, J=6.8 Hz, 3 H), 2.15 - 2.37 (m, 1 H), 2.29 (s, 3 H), 2.66 (t, J=6.2 Hz, 2 H), 3.03 (s, 3 H), 3.70 (t, J=6.2 Hz, 2 H), 3.98 (s, 3 H), 4.36 (d, J=7.5 Hz, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 6.82 (d, J=8.7 Hz, 1 H), 7.23 (d, J=8.7 Hz, 2 H), 7.30 - 7.46 (m, 2 H), 7.53 (d, J=1.9 Hz, 1 H), 7.79 (dd, J=8.5, 2.4 Hz, 1 H), 8.38 (d, J=2.4 Hz, 1 H).

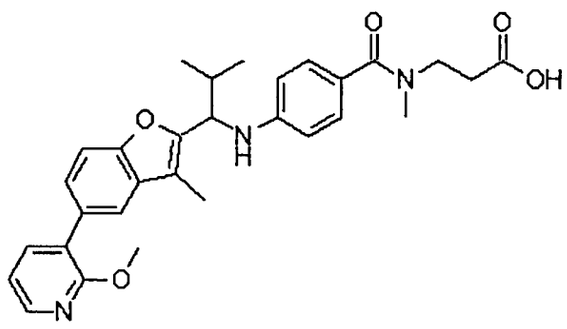
[1597]

Example A183

3-[{[4-({1-[5-(2-methoxypyridin-3-yl)-3-methyl-1-benzofuran-2-yl]-2-

methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1598]



[1599]

To a solution (10 mL) of ethyl 3-{[(4-{[1-(5-bromo-3-methyl-1-benzofuran-2-yl)-2-methylpropyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.55 g) synthesized in Example A182(2) in N,N-dimethylacetamide were added (2-methoxypyridin-3-yl)boronic acid (0.33 g), potassium carbonate (0.29 g) and tetrakistriphenylphosphine palladium (0.12 g), and the mixture was stirred at 70°C for 24 hr under argon atmosphere. The reaction mixture was cooled to room temperature, and filtered through celite, and the residue was washed with diethyl ether. Water was added to the filtrate, and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({1-[5-(2-methoxypyridin-3-yl)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.10 g) as a pale-yellow oil. The obtained oil was dissolved in ethanol (1 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.18 g, 33%) as a colorless solid.

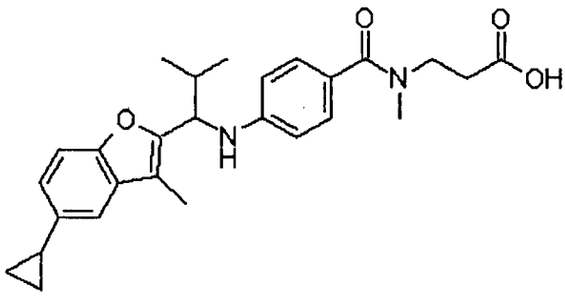
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 (d, J=6.4 Hz, 3 H), 1.15 (d, J=6.4 Hz, 3 H), 2.12 - 2.40 (m, 1 H), 2.27 (s, 3 H), 2.67 (t, J=6.2 Hz, 2 H), 3.04 (s, 3 H), 3.70 (t, J=6.2 Hz, 2 H), 3.96 (s, 3 H), 4.36 (d, J=7.9 Hz, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 6.97 (dd, J=7.2, 4.9 Hz, 1 H), 7.23 (d, J=8.7 Hz, 2 H), 7.33 - 7.77 (m, 4 H), 8.16 (dd, J=4.9, 1.9 Hz, 1 H).

[1600]

Example A184

3-{[(4-{[1-(5-cyclopropyl-3-methyl-1-benzofuran-2-yl)-2-methylpropyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1601]



[1602]

(1)1-(5-cyclopropyl-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-one

To a solution (20 mL) of 1-(5-bromo-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-one (1.0 g) synthesized in Example A182(1) in toluene were added cyclopropaneboronic acid (0.92 g), 2N aqueous sodium carbonate solution (5.3 mL), and the mixture was stirred at room temperature for 10 min under argon atmosphere. To the reaction mixture were added 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl(0.18 g) and tris(dibenzylideneacetone)dipalladium (0) (0.10 g), and the mixture was heated under reflux under argon atmosphere overnight. The reaction mixture was cooled to room temperature, and filtered through celite, and the residue was washed with diethyl ether. Water was added to the filtrate, and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography

(ethyl acetate:hexane=1:10, volume ratio) to give the title object compound (0.80 g, 93%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.59 - 1.08 (m, 4 H), 1.23 (d, J=6.8 Hz, 6 H), 1.91 - 2.11 (m, 1 H), 2.35 (s, 1 H), 2.58 (s, 3 H), 7.07 - 7.51 (m, 3 H).

[1603]

(2)1-(5-cyclopropyl-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-ol

1-(5-Cyclopropyl-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-one (0.80 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (10 mL) and methanol (1 mL), and sodium borohydride (90%, 0.34 g) was added to the solution under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (1 mL) and 1N hydrochloric acid (5 mL) were carefully added to the mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (0.4 g, 50%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.63 - 0.75 (m, 2 H), 0.80 (d, J=6.8 Hz, 3 H), 0.88 - 1.01 (m, 2 H), 1.11 (d, J=6.8 Hz, 3 H), 1.20 - 1.30 (m, 1 H), 1.93 - 2.03 (m, 1 H), 2.12 - 2.30 (m, 4 H), 4.46 (d, J=8.3 Hz, 1 H), 7.01 (dd, J=8.3, 1.9 Hz, 1 H), 7.17 (d, J=1.9 Hz, 1 H), 7.29 (d, J=8.3 Hz, 1 H).

[1604]

(3)3-{[(4-{[1-(5-cyclopropyl-3-methyl-1-benzofuran-2-yl)-2-methylpropyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a solution (5 mL) of 1-(5-cyclopropyl-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-ol (0.40 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added thionyl chloride (0.22 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (5

mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (5 mL), sodium iodide (0.373 g), sodium carbonate (0.25 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.41 g) synthesized in Example 2(2) were added to the solution, and the mixture was stirred at 70°C for 12 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-{[(4-{[1-(5-cyclopropyl-3-methyl-1-benzofuran-2-yl)-2-methylpropyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.25 g) as a pale-yellow oil. The obtained oil was dissolved in ethanol (2 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.24 g, 32%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.62 - 0.73 (m, 2 H), 0.82 - 1.00 (m, 5 H), 1.12 (d, J=6.8 Hz, 3 H), 1.90 - 2.07 (m, 1 H), 2.14 - 2.32 (m, 4 H), 2.67 (t, J=6.2 Hz, 2 H), 3.03 (s, 3 H), 3.70 (t, J=6.2 Hz, 2 H), 4.32 (d, J=7.9 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.98 (dd, J=8.7, 1.9 Hz, 1 H), 7.13 (d, J=1.9 Hz, 1 H), 7.19 - 7.25 (m, 3 H).

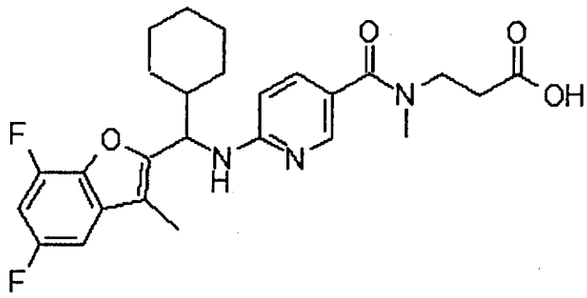
[1605]

Example A185

3-{[(6-{[cyclohexyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-yl)carbonyl](methyl)amino}propanoic acid

720

[1606]



[1607]

Cyclohexyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methanol (0.52 g) synthesized in Example A163(2) was dissolved in tetrahydrofuran (5 mL), and thionyl chloride (0.24 mL) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (3 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (5 mL), sodium iodide (0.45 g), sodium carbonate (0.30 g), ethyl 6-aminopyridine-3-carboxylate (0.45 g) were added to the solution, and the mixture was stirred at 60°C overnight. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 6-{[cyclohexyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridine-3-carboxylate (0.10 g) as a yellow oil. The obtained oil was dissolved in tetrahydrofuran (2 mL) and ethanol (2 mL), and the mixture was stirred in the presence of 1N aqueous sodium hydroxide solution (2 mL) at 100°C for 12 hr. The reaction mixture was allowed to cool to room temperature, and concentrated under reduced pressure. The

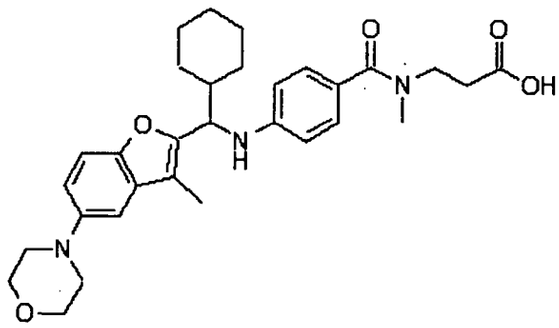
residue was dissolved in N,N-dimethylformamide (20 mL), ethyl 3-(methylamino)propanoate (0.24 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.48 g) and hydroxybenzotriazole monohydrate (0.38 g) were added to the solution, and the mixture was stirred at 70°C for 4 hr. The reaction mixture was allowed to cool to room temperature, water was added and the mixture was extracted with diethyl ether. The extract was washed with saturated brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, ethanol (5 mL) and 1N aqueous sodium hydroxide solution (1.0 mL) were added to the residue, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, neutralized with 1N hydrochloric acid (1.0 mL), and extracted with ethyl acetate. The extract was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (0.05 g, 6%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.00 - 1.93 (m, 11 H), 2.22 (s, 3 H), 2.68 - 2.75 (m, 2 H), 3.09 (s, 3 H), 3.70 - 3.80 (m, 2 H), 4.10 - 4.20 (m, 1 H), 6.36 (d, J=8.7 Hz, 1 H), 6.69 - 6.94 (m, 2 H), 7.50 - 7.58 (m, 1 H), 8.15 (d, J=1.9 Hz, 1 H).

[1608]

Example A186

3-[{[4-({cyclohexyl[3-methyl-5-(morpholin-4-yl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1609]



[1610]

(1) methyl 5-bromo-3-methyl-1-benzofuran-2-carboxylate

To a solution (200 mL) of 1-(5-bromo-2-hydroxyphenyl)ethanone (25.0 g) in N,N-dimethylformamide were added potassium carbonate (24.0 g) and methyl bromoacetate (11.5 mL) at room temperature, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was filtered, 1,8-diazabicyclo[5.4.0]undec-7-ene (23.2 mL) was added to the filtrate, and the mixture was stirred at 100°C for 3 hr. The reaction mixture was allowed to cool to room temperature, and ice water was added. The precipitate was washed with ethanol-water to give the title object compound (16.8 g, 52%) as a pale-red solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.56 (s, 3 H), 3.99 (s, 3 H), 7.36 - 7.46 (m, 1 H), 7.49 - 7.60 (m, 1 H), 7.77 (d, J=2.3 Hz, 1 H).

[1611]

(2) methyl 3-methyl-5-(morpholin-4-yl)-1-benzofuran-2-carboxylate

To a solution (100 mL) of methyl 5-bromo-3-methyl-1-benzofuran-2-carboxylate (5.4 g) synthesized in the above-mentioned (1) in toluene were added morpholine (5.2 mL), cesium carbonate (13.0 g), tris(dibenzylideneacetone)dipalladium (0) (0.92 g) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (1.1 g), and the mixture was heated under reflux under argon atmosphere for 20 hr. The reaction mixture was cooled to room temperature, and filtered through celite. Water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was concentrated, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.69 g, 13%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.57 (s, 3 H), 3.06 - 3.22 (m, 4 H), 3.83 - 3.94 (m, 4 H), 3.97 (s, 3 H), 7.02 (d, J=2.3 Hz, 1

H), 7.15 (dd, J=9.0, 2.3 Hz, 1 H), 7.45 (d, J=9.0 Hz, 1 H).

[1612]

(3)3-methyl-5-(morpholin-4-yl)-1-benzofuran-2-carbaldehyde

A solution (2 mL) of methyl 3-methyl-5-(morpholin-4-yl)-1-benzofuran-2-carboxylate (0.69 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added to an ice-cooled solution (5 mL) of lithium aluminum hydride (0.25 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (0.65 mL), 1N aqueous sodium hydroxide solution (3.2 mL) and water (0.65 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (0.48 g) of [3-methyl-5-(morpholin-4-yl)-1-benzofuran-2-yl]methanol as a pale-yellow oil. The obtained oil was dissolved in acetonitrile (5 mL), tetrapropylammonium perruthenate (0.07 g) and N-methylmorpholine N-oxide (0.46 g) were added to the solution at room temperature, and the mixture was stirred for 30 min. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.24 g, 40%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.59 (s, 3 H), 3.09 - 3.22 (m, 4 H), 3.79 - 3.98 (m, 4 H), 7.05 (d, J=2.3 Hz, 1 H), 7.23 (dd, J=9.2, 2.3 Hz, 1 H), 7.46 (d, J=9.2 Hz, 1 H), 10.00 (s, 1 H).

[1613]

(4)cyclohexyl[3-methyl-5-(morpholin-4-yl)-1-benzofuran-2-yl]methanol

To a solution (5 mL) of 3-methyl-5-(morpholin-4-yl)-1-benzofuran-2-carbaldehyde (0.24 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added dropwise cyclohexylmagnesium bromide (2 mL, 1M tetrahydrofuran solution) under ice-cooling. After the completion of the dropwise addition, the ice bath was removed, and the mixture

was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give cyclohexyl[3-methyl-5-(morpholin-4-yl)-1-benzofuran-2-yl]methanol (0.39 g, quantitative) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.07 - 2.01 (m, 12 H), 2.19 (s, 3 H), 3.11 - 3.21 (m, 4 H), 3.83 - 3.95 (m, 4 H), 4.50 (d, J=8.7 Hz, 1 H), 6.90 - 7.01 (m, 2 H), 7.33 (d, J=9.8 Hz, 1 H).

[1614]

(5)3-[{[4-({cyclohexyl[3-methyl-5-(morpholin-4-yl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (5 mL) of cyclohexyl[3-methyl-5-(morpholin-4-yl)-1-benzofuran-2-yl]methanol (0.39 g) synthesized in the above-mentioned (4) in tetrahydrofuran was added thionyl chloride (0.13 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (5 mL) was carefully added. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (5 mL), sodium iodide (0.23 g), sodium carbonate (0.15 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.25 g) synthesized in Example 2(2) were added to the solution and the mixture was stirred at 70°C for 15 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[3-methyl-5-

(morpholin-4-yl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.25 g) as a pale-yellow oil. The obtained oil was dissolved in ethanol (2 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.19 g, 33%) as a colorless solid.

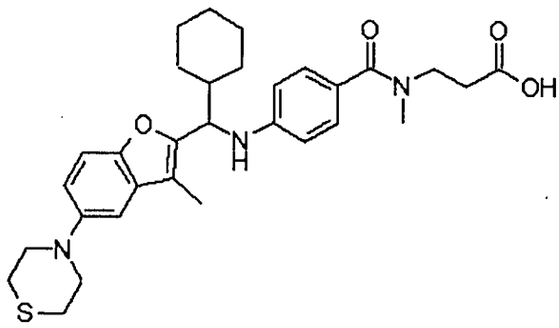
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 2.16 (m, 11 H), 2.22 (s, 3 H), 2.68 (br. s., 2 H), 3.04 (s, 3 H), 3.14 (br. s., 4 H), 3.58 - 3.77 (m, 2 H), 3.89 (br. s., 4 H), 4.36 (d, J=8.3 Hz, 1 H), 6.56 (d, J=9.0 Hz, 2 H), 6.84 - 7.02 (m, 2 H), 7.17 - 7.27 (m, 3 H).

[1615]

Example A187

3-[{[4-({cyclohexyl[3-methyl-5-(thiomorpholin-4-yl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1616]



[1617]

(1)cyclohexyl[3-methyl-5-(thiomorpholin-4-yl)-1-benzofuran-2-yl]methanone

To a solution (15 mL) of (5-bromo-3-methyl-1-benzofuran-2-yl)(cyclohexyl)methanone (0.75 g) synthesized in Example A174(1) in toluene were added thiomorpholine (0.72 g), cesium

carbonate (2.3 g), tris(dibenzylideneacetone)dipalladium (0) (0.16 g) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.2 g), and the mixture was heated under reflux under argon atmosphere for 18 hr. The reaction mixture was cooled to room temperature and filtered through celite, water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was concentrated to give a crude product (0.83 g, quantitative) of the title object compound as a yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.37 - 2.01 (m, 10 H), 2.56 (s, 3 H), 2.70 - 2.88 (m, 4 H), 3.25 - 3.40 (m, 1 H), 3.42 - 3.70 (m, 4 H), 7.00 - 7.78 (m, 3 H).

[1618]

(2)cyclohexyl[3-methyl-5-(thiomorpholin-4-yl)-1-benzofuran-2-yl]methanol

Cyclohexyl[3-methyl-5-(thiomorpholin-4-yl)-1-benzofuran-2-yl]methanone (0.83 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (10 mL) and methanol (1 mL), and sodium borohydride (90%, 0.2 g) was added to the solution under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (1 mL) and 1N hydrochloric acid (5 mL) were carefully added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (0.18 g, 22%) as a yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.81 - 1.93 (m, 11 H), 2.20 (s, 3 H), 2.70 - 2.91 (m, 4 H), 3.34 - 3.53 (m, 4 H), 4.50 (d, J=8.3 Hz, 1 H), 4.99 (t, J=6.4 Hz, 1 H), 6.90 - 7.40 (m, 3 H).

[1619]

(3)3-[{[4-({cyclohexyl[3-methyl-5-(thiomorpholin-4-yl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution (5 mL) of cyclohexyl[3-methyl-5-

(thiomorpholin-4-yl)-1-benzofuran-2-yl]methanol (0.18 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added thionyl chloride (0.07 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (5 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (5 mL), sodium iodide (0.15 g), sodium carbonate (0.10 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.13 g) synthesized in Example 2(2) were added to the solution, and the mixture was stirred at 70°C for 15 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[{[4-({cyclohexyl[3-methyl-5-(thiomorpholin-4-yl)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (0.08 g) as a pale-yellow oil. The obtained oil was dissolved in ethanol (2 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.05 g, 18%) as a colorless solid.

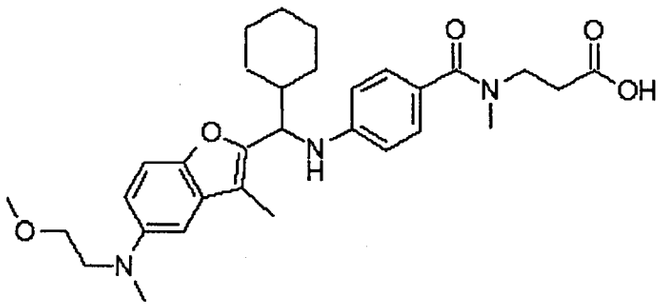
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.88 - 2.17 (m, 11 H), 2.20 (s, 3 H), 2.59 (br. s., 2 H), 2.80 - 3.20 (m, 7 H), 3.50 - 3.70 (m, 6 H), 4.38 (d, J=7.9 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 7.08 - 7.47 (m, 5 H).

[1620]

Example A188

3-[({4-[(cyclohexyl{5-[(2-methoxyethyl)(methyl)amino]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[1621]



[1622]

(1) methyl 5-[(2-methoxyethyl)(methyl)amino]-3-methyl-1-benzofuran-2-carboxylate

To a solution (50 mL) of methyl 5-bromo-3-methyl-1-benzofuran-2-carboxylate (2.7 g) synthesized in Example A186(1) in toluene were added 2-methoxy-N-methylethanamine (2.7 g), cesium carbonate (9.8 g), tris(dibenzylideneacetone)dipalladium (0) (0.69 g) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.87 g), and the mixture was heated under reflux under argon atmosphere for 6 hr. The reaction mixture was cooled to room temperature, and filtered through celite, water was added to the filtrate, and the mixture was extracted with ethyl acetate. The extract was concentrated, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:4, volume ratio) to give the title object compound (2.7 g, quantitative) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.55 (s, 3 H), 3.01 (s, 3 H), 3.37 (s, 3 H), 3.40 - 3.70 (m, 4 H), 3.97 (s, 3 H), 6.77 - 7.15 (m, 3 H).

[1623]

(2)5-[(2-methoxyethyl)(methyl)amino]-3-methyl-1-benzofuran-2-carbaldehyde

A solution (10 mL) of methyl 5-[(2-

729

methoxyethyl)(methyl)amino]-3-methyl-1-benzofuran-2-carboxylate (2.7 g) synthesized in the above-mentioned (1) in tetrahydrofuran was added to an ice-cooled solution (40 mL) of lithium aluminum hydride (0.38 g) in tetrahydrofuran. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (1.0 mL), 1N aqueous sodium hydroxide solution (5.0 mL) and water (1.0 mL) were successively added dropwise to quench the reaction. The residue was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (0.41 g) of {5-[(2-methoxyethyl)(methyl)amino]-3-methyl-1-benzofuran-2-yl}methanol as a pale-yellow oil. The obtained oil was dissolved in acetonitrile (20 mL), tetrapropylammonium perruthenate (0.07 g) and N-methylmorpholine N-oxide (0.46 g) were added to the solution at room temperature, and the mixture was stirred for 30 min. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.09 g, 3%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.58 (s, 3 H), 3.02 (s, 3 H), 3.38 (s, 3 H), 3.47 - 3.66 (m, 4 H), 6.81 (d, J=2.6 Hz, 1 H), 7.10 (dd, J=9.0, 2.6 Hz, 1 H), 7.40 (d, J=9.0 Hz, 1 H), 9.97 (s, 1 H).

[1624]

(3)cyclohexyl{5-[(2-methoxyethyl)(methyl)amino]-3-methyl-1-benzofuran-2-yl}methanol

To a solution (5 mL) of 5-[(2-methoxyethyl)(methyl)amino]-3-methyl-1-benzofuran-2-carbaldehyde (0.09 g) synthesized in the above-mentioned (2) in tetrahydrofuran was added dropwise cyclohexylmagnesium bromide (2 mL, 1M tetrahydrofuran solution) under ice-cooling. After the completion of the dropwise addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous ammonium

chloride solution, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:2, volume ratio) to give the title object compound (0.11 g, quantitative) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.99 - 1.96 (m, 12 H), 2.18 (s, 3 H), 2.99 (s, 3 H), 3.37 (s, 3 H), 3.45 - 3.72 (m, 4 H), 4.49 (d, J=8.7 Hz, 1 H), 6.77 - 7.30 (m, 3 H).

[1625]

(4)3-[({4-[(cyclohexyl{5-[(2-methoxyethyl)(methyl)amino]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

To a solution (10 mL) of cyclohexyl{5-[(2-methoxyethyl)(methyl)amino]-3-methyl-1-benzofuran-2-yl}methanol (0.11 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added thionyl chloride (0.10 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (5 mL) was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (10 mL), sodium iodide (0.14 g), sodium carbonate (0.09 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.15 g) synthesized in Example 2(2) were added to the solution, and the mixture was stirred at 70°C for 4 hr. After allowing to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give ethyl 3-[({4-[(cyclohexyl{5-[(2-methoxyethyl)(methyl)amino]-3-methyl-1-benzofuran-2-

yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoate (0.03 g) as a pale-yellow oil. The obtained oil was dissolved in ethanol (2 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.02 g, 11%) as a colorless solid.

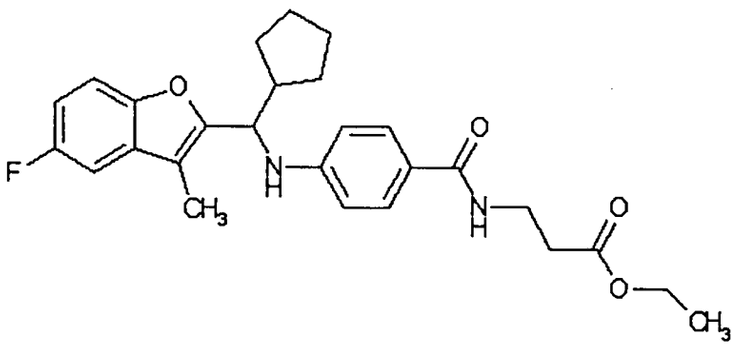
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 - 2.13 (m, 11 H), 2.21 (s, 3 H), 2.68 (br. s., 2 H), 2.98 (s, 3 H), 3.05 (s, 3 H), 3.36 (s, 3 H), 3.41 - 3.62 (m, 4 H), 3.68 (br. s., 2 H), 4.35 (d, J=8.0 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.67 - 6.88 (m, 2 H), 7.13 - 7.25 (m, 3 H).

[1626]

Example A189

ethyl 3-{[(4-{[cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate

[1627]



[1628]

(1) methyl 4-{[(E)-cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methylidene]amino}benzoate

To a mixture of cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methanone (1.3 g) synthesized in Example A67(3), methyl 4-aminobenzoate (798 mg), triethylamine (5.88 mL) and dichloromethane (13 mL) was added titanium (IV) chloride (1.0M dichloromethane solution, 6.3 mL) at 0°C, and the mixture was stirred at room temperature for 2 hr under

nitrogen atmosphere. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction. The solvent was concentrated under reduced pressure, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark brown solid. To a solution of the obtained solid in tetrahydrofuran (20 mL) were added sodium cyanoborohydride (657 mg) and acetic acid (1.50 mL), and the mixture was stirred at room temperature for 16 hr. Saturated aqueous sodium hydrogen carbonate solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 90:10) to give the title compound (1.27 g, 63%) as a yellow amorphous compound.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.49 - 1.69 (m, 8 H), 2.26 (s, 3 H), 2.43 - 2.56 (m, 1 H), 3.82 (s, 3 H), 4.34 - 4.45 (m, 1 H), 4.55 (d, J=8.3 Hz, 1 H), 6.56 (d, J=9.0 Hz, 2 H), 6.86 - 6.98 (m, 1 H), 7.02 - 7.14 (m, 1 H), 7.23 - 7.35 (m, 1 H), 7.79 (d, J=9.0 Hz, 2 H).

[1629]

(2)4-{[(E)-cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methylidene]amino}benzoic acid

To a mixture of methyl 4-{[(E)-cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methylidene]amino}benzoate (1.19 g) synthesized above, tetrahydrofuran (6 mL) and ethanol (6 mL) was added 1N aqueous sodium hydroxide solution (6 mL), and the mixture was stirred with heating under reflux for 3.5 hr. 1N Aqueous sodium hydroxide solution (6 mL) was additionally added to the mixture, and the mixture was stirred with heating under reflux for 14 hr. The reaction mixture was concentrated under reduced pressure, 1N hydrochloric acid (11 mL) was added to the residue, and the mixture was extracted with ethyl

acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title compound (1.08 g, 94%) as a colorless amorphous form.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.39 - 1.76 (m, 8 H), 1.89 - 1.99 (m, 1 H), 2.24 (s, 3 H), 2.40 - 2.55 (m, 1 H), 4.40 (d, J=9.1 Hz, 1 H), 6.52 (d, J=8.7 Hz, 2 H), 6.82 - 6.98 (m, 1 H), 7.02 - 7.13 (m, 1 H), 7.03 - 7.11 (m, 1 H), 7.22 - 7.29 (m, 1 H), 7.81 (d, J=8.7 Hz, 2 H).

[1630]

(3) ethyl 3-{[(4-{[cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate

A solution of 4-{[(E)-cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methylidene]amino}benzoic acid (483 mg) synthesized above, β-alanine ethyl ester hydrochloride (241 mg), 1-hydroxybenzotriazole monohydrate (240 mg), triethylamine (438 μL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (301 mg) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 3 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 60:40, v/v) to give the title compound (397 mg, 65%) as a colorless amorphous form.

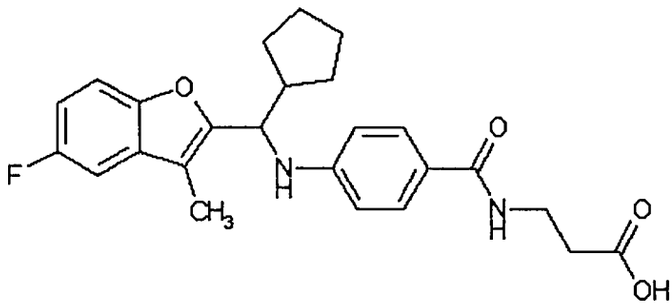
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.21 - 1.31 (m, 3 H), 1.50 - 1.70 (m, 8 H), 1.92 - 2.01 (m, 1 H), 2.25 (s, 3 H), 2.42 - 2.55 (m, 1 H), 2.58 (t, J=5.9 Hz, 2 H), 3.65 (q, J=6.1 Hz, 2 H), 4.31 - 4.49 (m, 2 H), 6.57 (d, J=8.7 Hz, 3 H), 6.84 - 6.98 (m, 1 H), 7.06 (dd, J=8.3, 2.7 Hz, 1 H), 7.21 - 7.32 (m, 1 H), 7.54 (d, J=8.7 Hz, 2 H).

[1631]

Example A190

3-{[(4-{[cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoic acid

[1632]



[1633]

Ethyl 3-{[(4-{[cyclopentyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl]amino}propanoate (363 mg) synthesized in Example A189 was dissolved in ethanol (1.5 mL) and tetrahydrofuran (1.5 mL), 1N aqueous sodium hydroxide solution (1.5 mL) was added to the solution, and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure, water (4 mL) was added to the mixture, and the mixture was neutralized with 1N hydrochloric acid under ice-cooling, and the mixture was stirred for 30 min. The resulting precipitate was collected by filtration, and dried to give the title compound (283 mg, 83%) as a colorless solid.

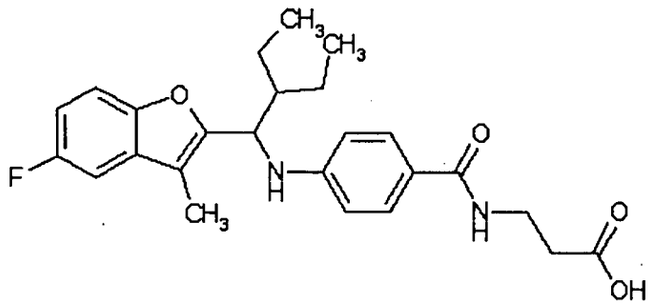
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.21 - 1.72 (m, 7 H), 1.91 - 2.04 (m, 1 H), 2.24 (s, 3 H), 2.47 (q, J=8.1 Hz, 1 H), 2.62 (t, J=5.9 Hz, 2 H), 3.63 (q, J=6.1 Hz, 2 H), 4.38 (d, J=9.1 Hz, 1 H), 6.51 - 6.64 (m, 3 H), 6.86 - 6.97 (m, 1 H), 7.06 (dd, J=8.5, 2.5 Hz, 1 H), 7.19 - 7.32 (m, 2 H), 7.52 (d, J=8.7 Hz, 2 H).

[1634]

Example A191

3-{[(4-{[2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl]amino}propanoic acid

[1635]



[1636]

A solution of 4-{[2-ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}benzoic acid (180 mg) synthesized in Example A71(4), β-alanine ethyl ester hydrochloride (89 mg), 1-hydroxybenzotriazole monohydrate (89 mg), triethylamine (163 μL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (111 mg) in N,N-dimethylformamide (5 mL) was stirred at room temperature for 6 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 60:40, v/v) to give a colorless oil (159 mg). The obtained colorless oil (159 mg) was dissolved in ethanol (1.0 mL) and tetrahydrofuran (1.0 mL), 1N aqueous sodium hydroxide solution (0.66 mL) was added to the solution, and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure, water (4 mL) was added, neutralized with 1N hydrochloric acid under ice-cooling, and the mixture was stirred for 30 min. The resulting precipitate was collected by filtration, and dried to give the title compound (87 mg, 41%) as a colorless solid.

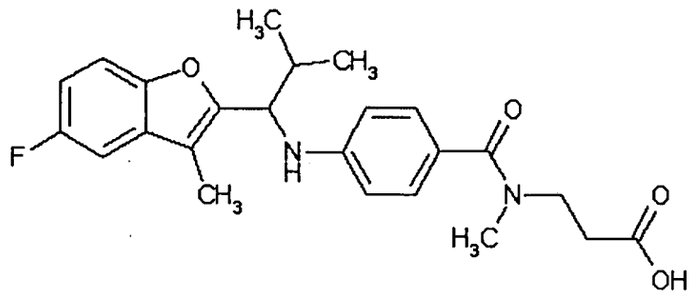
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 (t, J=7.4 Hz, 3 H), 0.94 (t, J=7.6 Hz, 3 H), 1.14 - 1.68 (m, 4 H), 1.80 - 1.92 (m, 1 H), 2.21 (s, 3 H), 2.63 (t, J=5.7 Hz, 2 H), 3.64 (q, J=6.1 Hz, 2 H), 4.58 (d, J=7.6 Hz, 1 H), 6.49 - 6.64 (m, 3 H), 6.92 (td, J=9.1, 2.7 Hz, 1 H), 7.05 (dd, J=8.5, 2.5 Hz, 1 H), 7.22 - 7.29 (m, 1 H), 7.53 (d, J=8.7 Hz, 2 H).

[1637]

Example A192

3-{[(4-{[1-(5-fluoro-3-methyl-1-benzofuran-2-yl)-2-methylpropyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1638]



[1639]

(1)1-(5-fluoro-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-one

To a solution of 5-fluoro-3-methyl-1-benzofuran (2.0 g) synthesized in Example A67(2) and isobutyryl chloride (1.56 g) in nitromethane (40 mL) was added aluminum chloride (anhydrous) (2.66 g) at 0°C, and the mixture was stirred at 0°C for 1 hr, and at room temperature for 12 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 90:10, v/v) to give the title compound (1.933 g, 66%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.24 (d, J=7.2 Hz, 6 H), 2.57 (s, 3 H), 3.44 - 3.65 (m, 1 H), 7.11 - 7.33 (m, 2 H), 7.41 - 7.50 (m, 1 H)

[1640]

(2)1-(5-fluoro-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-ol

1-(5-Fluoro-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-one (11.66 g) synthesized above was dissolved in methanol (4 mL)-tetrahydrofuran (20 mL), and sodium tetrahydroborate

(90%)(446 mg) was added to the solution at 0°C. The reaction mixture was stirred at 0°C for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give the title compound (1.193 g, 100%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.82 (d, J=6.8 Hz, 3 H), 1.12 (d, J=6.8 Hz, 3 H), 1.99 - 2.06 (m, 1 H), 2.15 - 2.27 (m, 4 H), 4.43 - 4.52 (m, 1 H), 6.91 - 7.01 (m, 1 H), 7.11 (dd, J=8.7, 2.6 Hz, 1 H), 7.33 (dd, 1 H).

[1641]

(3)3-{[(4-{[1-(5-fluoro-3-methyl-1-benzofuran-2-yl)-2-methylpropyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a solution of 1-(5-fluoro-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-ol (1.128 g) obtained above in tetrahydrofuran (10 mL) was added thionyl chloride (0.45 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 hr. To the reaction mixture was added aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give a crude 2-(1-chloro-2-methylpropyl)-5-fluoro-3-methyl-1-benzofuran (1.10 g). To the obtained 2-(1-chloro-2-methylpropyl)-5-fluoro-3-methyl-1-benzofuran (500 mg) were added ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (546 mg) obtained in Example 2 (2), sodium iodide (623 mg), sodium carbonate (441 mg) and N,N-dimethylformamide (5 mL), and the mixture was stirred at 80°C for 13 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration,

the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 50:50, v/v) to give a yellow amorphous compound (287 mg). The obtained amorphous compound (280 mg) was dissolved in ethanol (2.4 mL) and tetrahydrofuran (2.4 mL), and 1N aqueous sodium hydroxide solution (1.2 mL) was added to the solution, and the mixture was stirred at room temperature for 1.5 hr. The solvent was evaporated under reduced pressure, water (4 mL) was added, the mixture was neutralized with 1N hydrochloric acid (1.2 mL) under ice-cooling, and the mixture was stirred for 1.5 hr. The resulting precipitate was collected by filtration, and dried to give the title compound (231 mg, 23%) as a yellow amorphous compound.

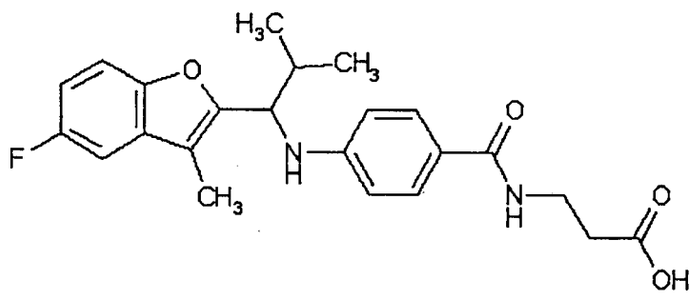
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, 3 H), 1.13 (d, J=6.4 Hz, 3 H), 2.18 - 2.30 (m, 4 H), 2.66 (t, J=6.4 Hz, 2 H), 3.03 (s, 3 H), 3.70 (t, J=6.6 Hz, 2 H), 4.33 (d, J=7.5 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.93 (td, J=9.0, 2.6 Hz, 1 H), 7.07 (dd, J=8.7, 2.6 Hz, 1 H), 7.22 - 7.32 (m, 3 H).

[1642]

Example A193

3-{[(4-{[1-(5-fluoro-3-methyl-1-benzofuran-2-yl)-2-methylpropyl]amino}phenyl)carbonyl]amino}propanoic acid

[1643]



[1644]

To a solution of 1-(5-fluoro-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-ol (1.128 g) obtained in Example A192(2) in tetrahydrofuran (10 mL) was added thionyl chloride (0.45 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 hr. To the reaction mixture was added

aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give a crude 2-(1-chloro-2-methylpropyl)-5-fluoro-3-methyl-1-benzofuran (1.10 g). To the obtained 2-(1-chloro-2-methylpropyl)-5-fluoro-3-methyl-1-benzofuran (485 mg) were added ethyl 3-{[(4-aminophenyl)carbonyl]amino}propanoate (500 mg) obtained in Example 1(2), sodium iodide (599 mg), sodium carbonate (424 mg) and N,N-dimethylformamide (5 mL) and the mixture was stirred at 80°C for 13 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 50:50, v/v) to give a colorless amorphous compound (123 mg). The obtained amorphous compound (123 mg) was dissolved in ethanol (2.0 mL) and tetrahydrofuran (2.0 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution, and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure, water (4 mL) was added to the residue, and the mixture was neutralized with 1N hydrochloric acid (1.0 mL) under ice-cooling and the mixture was stirred for 20 min. The resulting precipitate was collected by filtration, and dried to give the title compound (97 mg, 11%) as a yellow amorphous compound.

$^1$H NMR (300 MHz, CHLOROFORM-d) δppm 0.91 (d, 3 H), 1.13 (d, J=6.8 Hz, 3 H), 2.18 - 2.29 (m, 4 H), 2.64 (t, J=5.7 Hz, 2 H), 3.65 (q, J=6.0 Hz, 2 H), 4.35 (d, J=7.9 Hz, 1 H), 6.57 (d, J=8.7 Hz, 3 H), 6.92 (td, J=9.0, 2.6 Hz, 1 H), 7.06 (dd, J=8.5, 2.4 Hz, 1 H), 7.23 - 7.30 (m, 1 H), 7.54 (d, J=8.7 Hz, 2 H).

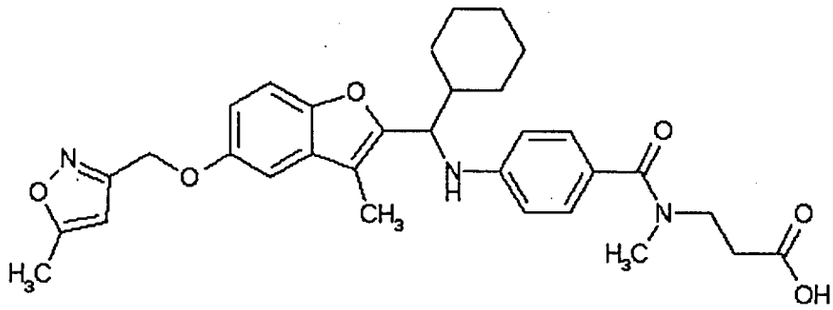
[1645]

Example A194

3-[({4-[(cyclohexyl{3-methyl-5-[(5-methylisoxazol-3-

yl)methoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[1646]



[1647]

(1)[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methanol

[5-(Benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methanone (23.4 g) synthesized in Example A82(2) was dissolved in methanol (40 mL)-tetrahydrofuran (400 mL), and sodium tetrahydroborate (90%)(5.64 g) was added to the solution at 0°C. The reaction mixture was stirred at 0°C for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give the title compound (25.17 g, 100%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.88 - 1.40 (m, 7 H), 1.61 - 1.70 (m, 2 H), 1.75 - 1.92 (m, 2 H), 1.95 - 1.99 (m, 1 H), 2.18 (s, 3 H), 4.45 - 4.54 (m, 1 H), 5.10 (s, 2 H), 6.94 (dd, J=9.0, 2.6 Hz, 1 H), 7.00 (d, J=2.3 Hz, 1 H), 7.28 - 7.49 (m, 6 H).

[1648]

(2)5-(benzyloxy)-2-[chloro(cyclohexyl)methyl]-3-methyl-1-benzofuran

To a solution of [5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methanol (25.17 g) synthesized above in tetrahydrofuran (250 mL) was added thionyl chloride (9.44 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 hr. To the reaction mixture was added

aqueous sodium hydrogen carbonate solution cooled to 0°C, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give the title compound (25.39 g, 96%) as a yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.87 - 1.52 (m, 6 H), 1.58 - 1.71 (m, 4 H), 2.19 (s, 3 H), 2.29 - 2.38 (m, 1 H), 4.80 (d, 1 H), 5.10 (s, 2 H), 6.94 - 7.02 (m, 2 H), 7.32 - 7.56 (m, 6 H).

[1649]

(3) ethyl 3-[{[4-({[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate

To 5-(benzyloxy)-2-[chloro(cyclohexyl)methyl]-3-methyl-1-benzofuran (8.48 g) obtained above were added ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (12.5 g) obtained in Example 2(2), sodium iodide (7.62 g), sodium carbonate (5.39 mg) and N,N-dimethylacetamide (125 mL), and the mixture was stirred at 60°C for 14 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 50:50, v/v) to give the title compound (14.20 g, 72%) as a yellow amorphous compound.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.88 - 1.26 (m, 5 H), 1.50 - 2.09 (m, 7 H), 2.21 (s, 3 H), 2.56 - 2.73 (m, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.0 Hz, 2 H), 4.06 - 4.18 (m, 2 H), 4.32 - 4.42 (m, 2 H), 4.32 - 4.39 (m, 2 H), 5.08 (s, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.86 - 6.92 (m, 1 H), 6.97 (d, J=2.3 Hz, 1 H), 7.17 - 7.53 (m, 8 H).

[1650]

(4) ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

Ethyl 3-[{[4-({[5-(benzyloxy)-3-methyl-1-benzofuran-2-yl](cyclohexyl)methyl}amino)phenyl]carbonyl}(methyl)amino]propanoate (10.11 g) obtained above was dissolved in ethanol (200 mL), and 10% palladium carbon (containing water)(1.0 g) was added to the solution at room temperature. The reaction mixture was stirred under hydrogen atmosphere (1 atm) at room temperature for 24 hr, and the catalyst was filtered off. The filtrate was concentrated under reduced pressure to give the title compound (8.98 g, 100%) as a brown amorphous compound. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.16 (m, 3 H), 1.22 - 1.27 (m, 5 H), 1.52 (d, J=12.5 Hz, 1 H), 1.65 - 1.95 (m, 4 H), 2.08 - 2.13 (m, 1 H), 2.15 (s, 3 H), 2.62 (t, J=6.8 Hz, 2 H), 3.02 (s, 3 H), 3.72 (t, J=7.0 Hz, 2 H), 4.05 - 4.17 (m, 2 H), 4.30 - 4.38 (m, 2 H), 5.58 (s, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.70 (dd, J=8.5, 2.5 Hz, 1 H), 6.80 (d, J=2.7 Hz, 1 H), 7.17 (d, J=8.7 Hz, 1 H), 7.22 (d, J=8.3 Hz, 2 H).

[1651]

(5)3-[({4-[(cyclohexyl{3-methyl-5-[(5-methylisoxazol-3-yl)methoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

A solution of ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (300 mg) obtained above, (5-methylisoxazol-3-yl)methanol (83 mg) and tributylphosphine (308 mg) in tetrahydrofuran (30 mL) was cooled to 0°C in an ice-bath, and 1,1'-(azodicarbonyl)dipiperidine (308 mg) was added to the solution. The reaction mixture was stirred at room temperature for 3.5 hr. (5-Methylisoxazol-3-yl)methanol (83 mg), tributylphosphine (154 mg) and 1,1'-(azodicarbonyl)dipiperidine (154 mg) were further added to the mixture, and the mixture was stirred at room temperature for 14 hr. To the reaction mixture was added hexane (60 mL). The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography

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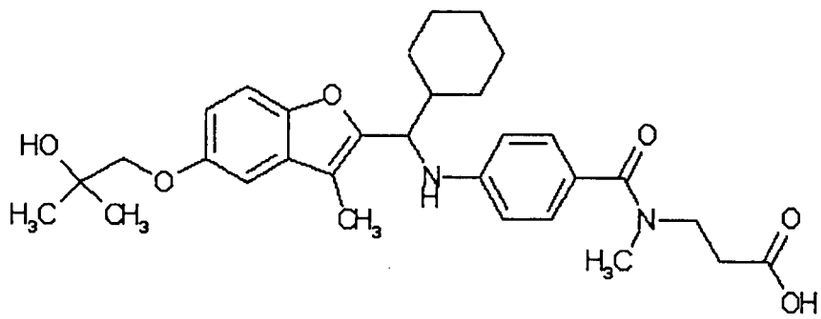
(hexane-ethyl acetate 100:0 - 50:50, v/v) to give a colorless amorphous compound (105 mg). The obtained colorless amorphous compound (105 mg) was dissolved in ethanol (0.5 mL) and tetrahydrofuran (0.5 mL), 1N aqueous sodium hydroxide solution (0.36 mL) was added to the solution, and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure, water (2 mL) was added to the residue, and the mixture was neutralized with 1N hydrochloric acid (0.36 mL) under ice-cooling. The resulting precipitate was collected by filtration, and dried to give the title compound (72 mg, 21%) as a colorless amorphous form. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.01 - 1.25 (m, 5 H), 1.42 - 1.83 (m, 6 H), 2.07 (br. s., 1 H), 2.21 (s, 3 H), 2.41 (s, 3 H), 2.61 - 2.69 (m, 2 H), 3.02 (s, 3 H), 3.68 (t, J=6.4 Hz, 2 H), 4.35 (d, J=7.9 Hz, 1 H), 5.13 (s, 2 H), 6.11 (s, 1 H), 6.55 (d, J=8.3 Hz, 2 H), 6.87 (dd, J=8.9, 2.4 Hz, 1 H), 6.97 (d, J=2.6 Hz, 1 H), 7.19 - 7.26 (m, 3 H).

[1652]

Example A195

3-[{[4-({cyclohexyl[5-(2-hydroxy-2-methylpropoxy)-3-methyl-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1653]




[1654]

A solution of ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (300 mg) obtained in Example A194(4), isobutylene oxide (439 mg), potassium carbonate (422 mg) and sodium iodide (457 mg) in

N,N-dimethylformamide (6 mL) was stirred at 80°C for 9 hr. Isobutylene oxide (2.0 g) was further added to the mixture, and the mixture was stirred at 120°C for 14 hr. Isobutylene oxide (2.0 g) was further added to the mixture, and the mixture was stirred at 120°C for 5 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 50:50, v/v) to give a colorless oil (103 mg). The obtained colorless oil (103 mg) was dissolved in ethanol (0.5 mL) and tetrahydrofuran (0.5 mL), 1N aqueous sodium hydroxide solution (0.36 mL) was added to the solution, and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure, water (4 mL) was added to the residue, and the mixture was neutralized with 1N hydrochloric acid (0.36 mL) under ice-cooling. The resulting precipitate was collected by filtration, and dried to give the title compound (88 mg, 26%) as a colorless solid.

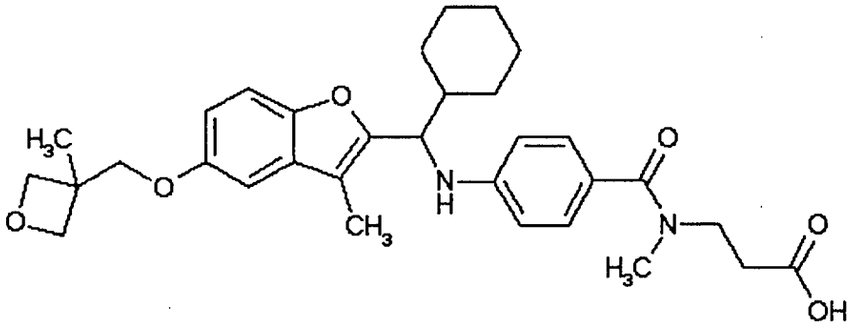
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 - 1.27 (m, 6 H), 1.35 (s, 6 H), 1.47 - 1.91 (m, 5 H), 2.04 - 2.13 (m, 1 H), 2.21 (s, 3 H), 2.62 (t, J=6.2 Hz, 2 H), 3.01 (s, 3 H), 3.67 (t, J=6.6 Hz, 2 H), 3.82 (s, 2 H), 4.35 (d, J=7.9 Hz, 1 H), 6.55 (d, J=9.0 Hz, 2 H), 6.84 (dd, J=8.7, 2.6 Hz, 1 H), 6.90 (d, J=2.3 Hz, 1 H), 7.22 (d, J=9.8 Hz, 2 H), 7.26 - 7.28 (m, 1 H).

[1655]

Example A196

3-[({4-[(cyclohexyl{3-methyl-5-[(3-methyloxetan-3-yl)methoxy]-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[1656]



[1657]

A solution of ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (300 mg) obtained in Example A194(4), (3-methyloxetan-3-yl)methanol (75 mg) and tributylphosphine (308 mg) in tetrahydrofuran (30 mL) was cooled to 0°C in an ice-bath, and 1,1'-(azodicarbonyl)dipiperidine (308 mg) was added to the solution. The reaction mixture was stirred at room temperature for 18 hr. To the reaction mixture was added hexane (60 mL). The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (NH silica, hexane-ethyl acetate 100:0 - 50:50, v/v), and then preparative HPLC" instrument: Gilson Inc., preparative HPLC system; column: Develosil ODS-UG-10, S-5 μm, 50 x 100 mm; solvent: SOLUTION A; 0.1% trifluoroacetic acid-containing water, SOLUTION B; 0.1% trifluoroacetic acid-containing acetonitrile, (SOLUTION A:SOLUTION B=95:5 - 0:100); flow rate: 150 mL/min; detection method: UV 220 nm". The fractionated fraction was concentrated and acetonitrile was evaporated. Saturated aqueous sodium hydrogen carbonate solution (0°C) was added to the aqueous layer, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give a colorless oil (100 mg). The obtained colorless oil (100 mg) was dissolved in ethanol (0.5 mL) and tetrahydrofuran (0.5 mL), 1N aqueous sodium hydroxide

solution (0.34 mL) was added to the solution, and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure, water (4 mL) was added to the residue, and the mixture was neutralized with 1N hydrochloric acid (0.34 mL) under ice-cooling and stirred at 0°C for 30 min. The resulting precipitate was collected by filtration, and dried to give the title compound (73 mg, 22%) as a colorless solid.

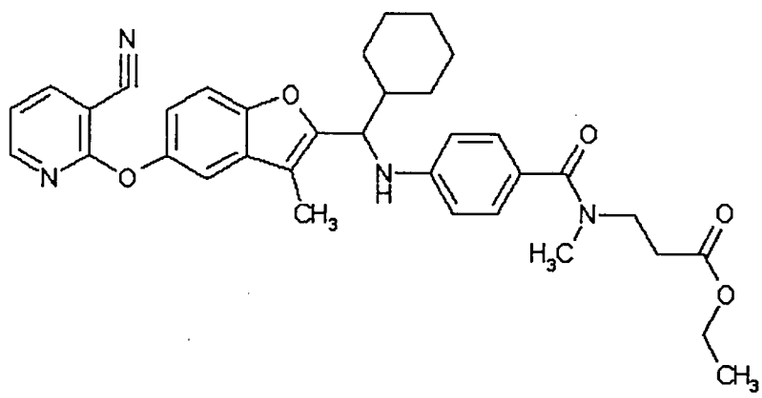
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 - 1.33 (m, 5 H), 1.45 (s, 3 H), 1.52 - 1.95 (m, 5 H), 2.09 (d, J=8.7 Hz, 1 H), 2.22 (s, 3 H), 2.55 - 2.74 (m, 2 H), 3.03 (s, 3 H), 3.65 - 3.76 (m, 3 H), 4.05 (s, 2 H), 4.36 (d, J=7.9 Hz, 1 H), 4.47 (d, J=6.0 Hz, 2 H), 4.64 (d, J=5.7 Hz, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.80 - 6.89 (m, 1 H), 6.92 (d, J=2.6 Hz, 1 H), 7.14 - 7.32 (m, 3 H).

[1658]

Example A197

ethyl 3-{[(4-{[{5-[(3-cyanopyridin-2-yl)oxy]-3-methyl-1-benzofuran-2-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate

[1659]



[1660]

A solution of ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (300 mg) obtained in Example A194(4), 2-chloro-3-cyanopyridine (126 mg) and potassium carbonate (125 mg) in N,N-dimethylformamide

(3 mL) was stirred at 80°C for 2.5 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 50:50, v/v) to give the title compound (250 mg, 69%) as a colorless amorphous form.

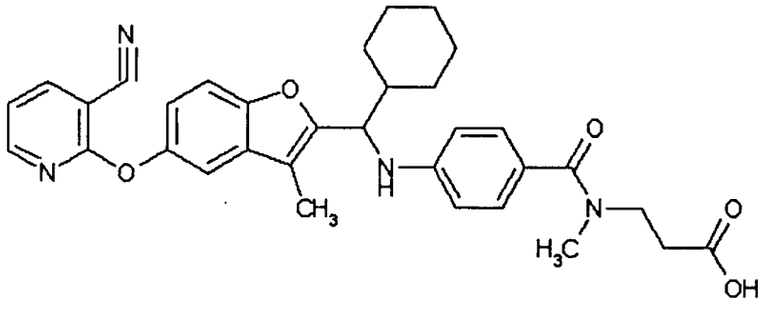
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.99 - 1.31 (m, 6 H), 1.48 - 1.96 (m, 6 H), 2.06 - 2.14 (m, 2 H), 2.23 (s, 3 H), 2.62 (t, J=7.0 Hz, 2 H), 3.02 (s, 3 H), 3.71 (t, J=7.0 Hz, 2 H), 4.12 (q, J=7.2 Hz, 2 H), 4.31 - 4.44 (m, 2 H), 6.56 (d, J=8.3 Hz, 2 H), 6.98 - 7.11 (m, 2 H), 7.19 - 7.25 (m, 3 H), 7.40 (d, J=8.7 Hz, 1 H), 8.00 (dd, J=7.6, 1.9 Hz, 1 H), 8.29 (dd, J=4.9, 1.9 Hz, 1 H).

[1661]

Example A198

3-{[(4-{[{5-[(3-cyanopyridin-2-yl)oxy]-3-methyl-1-benzofuran-2-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[1662]



[1663]

Ethyl 3-{[(4-{[{5-[(3-cyanopyridin-2-yl)oxy]-3-methyl-1-benzofuran-2-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (234 mg) obtained in Example A197 was dissolved in ethanol (1.5 mL) and tetrahydrofuran (1.5 mL), 1N aqueous sodium hydroxide solution (0.78 mL) was added to the solution, and the mixture was stirred at room temperature for 30 min.

The solvent was evaporated under reduced pressure, water (4 mL) was added, and the mixture was neutralized with 1N hydrochloric acid (0.78 mL) under ice-cooling. The resulting precipitate was collected by filtration and dried. The obtained residue was purified by preparative HPLC "instrument: Gilson Inc., preparative HPLC system; column: Develosil ODS-UG-10, S-5 μm, 50 x 100 mm; solvent: SOLUTION A; 0.1% trifluoroacetic acid-containing water, SOLUTION B; 0.1% trifluoroacetic acid-containing acetonitrile, (SOLUTION A:SOLUTION B=95:5 - 0:100); flow rate: 150 mL/min; detection method: UV 220 nm". To the fractionated fraction was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give the title compound (73 mg, 33%) as a colorless amorphous form.

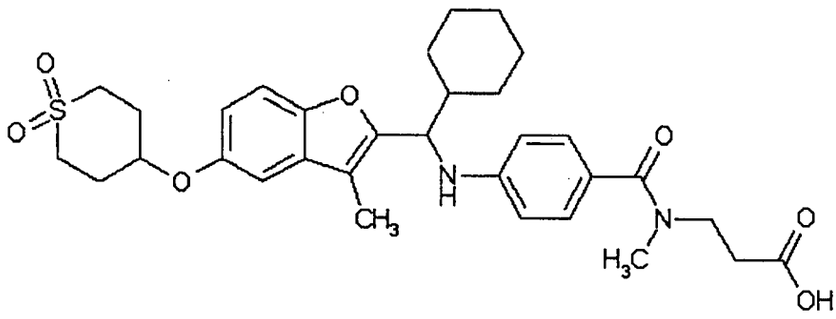
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.12 (br. s., 4 H), 1.42 - 1.91 (m, 6 H), 2.04 (s, 3 H), 2.20 (s, 3 H), 2.39 - 2.63 (m, 1 H), 2.89 - 3.03 (m, 3 H), 3.58 (m, 2 H), 4.37 (d, J=8.0 Hz, 1 H), 6.54 (d, J=8.3 Hz, 2 H), 6.94 - 7.10 (m, 2 H), 7.17 - 7.24 (m, 3 H), 7.37 (d, J=8.7 Hz, 1 H), 7.99 (dd, J=7.6, 1.9 Hz, 1 H), 8.28 (d, J=3.4 Hz, 1 H).

[1664]

Example A199

3-[({4-[(cyclohexyl{5-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)oxy]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

[1665]



[1666]

(1)1,1-dioxidotetrahydro-2H-thiopyran-4-yl 4-methylbenzenesulfonate

To a solution of tetrahydro-2H-thiopyran-4-yl 4-methylbenzenesulfonate (3.0 g) in acetic acid (9 mL) was added 30% hydrogen peroxide (3 mL), and the mixture was stirred at 50°C for 3.5 hr. The reaction mixture was cooled to room temperature, water (30 mL) was added to the mixture, and the mixture was stirred at 0°C for 5 min. The obtained solid was collected by filtration and washed with water to give the title compound (2.84 g, 85%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.26 - 2.36 (m, 4 H), 2.47 (s, 3 H), 2.84 - 3.00 (m, 2 H), 3.10 - 3.43 (m, 2 H), 4.74 - 4.86 (m, 1 H), 7.38 (d, J=8.0 Hz, 2 H), 7.81 (d, J=8.3 Hz, 2 H).

[1667]

(2)3-[({4-[(cyclohexyl{5-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)oxy]-3-methyl-1-benzofuran-2-yl}methyl)amino]phenyl}carbonyl)(methyl)amino]propanoic acid

A solution of ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (400 mg) obtained in Example A194(4), 1,1-dioxidotetrahydro-2H-thiopyran-4-yl 4-methylbenzenesulfonate (593 mg) synthesized above and tripotassium phosphate (223 mg) in N,N-dimethylformamide (4 mL) was stirred at 100°C for 14 hr. 1,1-Dioxidotetrahydro-2H-thiopyran-4-yl 4-methylbenzenesulfonate (593 mg) and tripotassium phosphate (112 mg) were further added to the mixture, and the mixture was stirred at 100°C for 2 hr then at 120°C for 3 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 34:66, v/v) to give a colorless amorphous form (200 mg). The

colorless amorphous form (200 mg) was dissolved in ethanol (1.5 mL) and tetrahydrofuran (1.5 mL), and 1N aqueous sodium hydroxide solution (0.64 mL) was added to the solution, and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure, water (4 mL) was added to the residue, and the mixture was neutralized with 1N hydrochloric acid (0.64 mL) under ice-cooling and stirred at 0°C for 30 min. The resulting precipitate was collected by filtration, and dried to give the title compound (136 mg, 29%) as a colorless amorphous form.

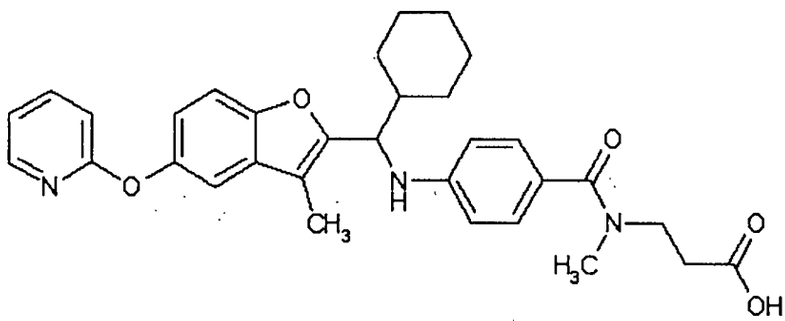
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.99 - 2.00 (m, 8 H), 2.21 (s, 3 H), 2.31 - 2.73 (m, 10 H), 2.86 - 2.99 (m, 1 H), 3.03 (s, 3 H), 3.36 - 3.53 (m, 2 H), 3.65 - 3.76 (m, 2 H), 4.36 (d, J=8.3 Hz, 1 H), 4.54 - 4.82 (m, 3 H), 6.55 (d, J=8.3 Hz, 2 H), 6.78 - 6.87 (m, 1 H), 6.93 (d, J=2.6 Hz, 1 H), 7.17 - 7.30 (m, 3 H).

[1668]

Example A200

3-[{[4-({cyclohexyl[3-methyl-5-(pyridin-2-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1669]



[1670]

A solution of ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (300 mg) obtained in Example A194(4), 2-fluoropyridine (88 mg) and potassium carbonate (126 mg) in N,N-dimethylformamide (3 mL) was stirred at 80°C for 8 hr then at room temperature for 48 hr. 2-Fluoropyridine (88 mg) was added to the mixture, and the mixture was stirred at 120°C for 4 hr. 2-Fluoropyridine (352

mg) was added to the mixture, and the mixture was stirred at 120°C for 10 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 50:50, v/v) to give a colorless oil (35 mg). The obtained oil (35 mg) was dissolved in tetrahydrofuran (0.5 mL), and 1N aqueous sodium hydroxide solution (0.12 mL) was added to the solution, and the mixture was stirred at 50°C for 1 hr. The solvent was evaporated under reduced pressure, water (4 mL) was added to the residue, and the mixture was neutralized with 1N hydrochloric acid (0.12 mL) under ice-cooling and stirred at 0°C for 20 min. The resulting precipitate was collected by filtration, and dried to give the title compound (22 mg, 7%) as a colorless amorphous form.

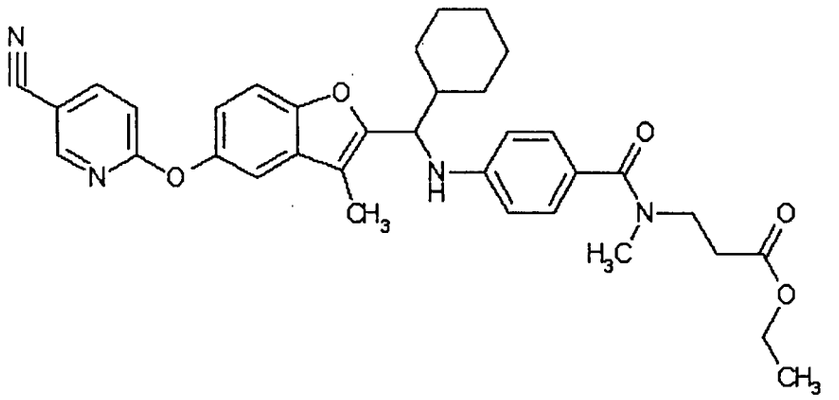
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 - 1.42 (m, 6 H), 1.51 - 1.96 (m, 5 H), 2.13 (br. s., 1 H), 2.19 (s, 3 H), 2.36 - 2.69 (m, 2 H), 3.01 (s, 3 H), 3.54 (br. s., 2 H), 4.39 (d, J=7.9 Hz, 1 H), 6.58 (d, J=8.7 Hz, 2 H), 6.88 - 7.05 (m, 3 H), 7.12 - 7.24 (m, 3 H), 7.33 (d, J=8.7 Hz, 1 H), 7.65 - 7.74 (m, 1 H), 8.09 - 8.20 (m, 1 H).

[1671]

Example A201

Ethyl 3-{[(4-{[{5-[(5-cyanopyridin-2-yl)oxy]-3-methyl-1-benzofuran-2-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate

[1672]



[1673]

A solution of ethyl 3-{[(4-{[cyclohexyl(5-hydroxy-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (400 mg) obtained in Example A194(4), 2-chloro-5-cyanopyridine (167 mg) and potassium carbonate (168 mg) in N,N-dimethylformamide (4 mL) was stirred at 80°C for 14 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 50:50, v/v) to give the title compound (340 mg, 70%) as a colorless amorphous form.

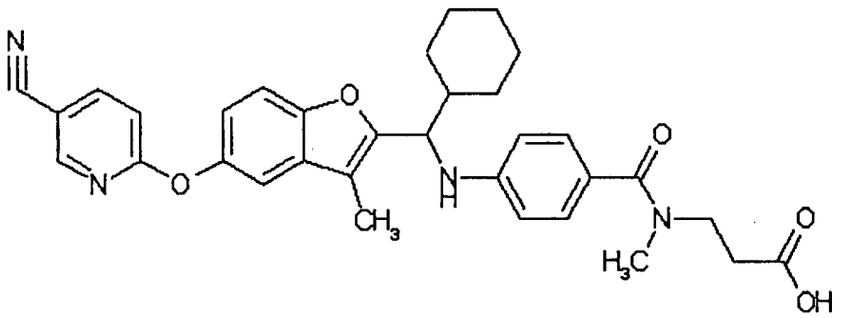
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.01 - 1.30 (m, 8 H), 1.55 - 1.96 (m, 5 H), 2.09 - 2.15 (m, 1 H), 2.22 (s, 3 H), 2.62 (t, J=6.8 Hz, 2 H), 3.03 (s, 3 H), 3.71 (t, J=7.0 Hz, 2 H), 4.04 - 4.18 (m, 2 H), 4.27 - 4.48 (m, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.90 - 7.07 (m, 2 H), 7.17 (d, J=2.3 Hz, 1 H), 7.22 (d, J=8.7 Hz, 2 H), 7.40 (d, J=8.7 Hz, 1 H), 7.90 (dd, J=8.7, 2.3 Hz, 1 H), 8.46 (d, J=2.3 Hz, 1 H).

[1674]

Example A202

3-{[(4-{[{5-[(5-cyanopyridin-2-yl)oxy]-3-methyl-1-benzofuran-2-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoic acid

[1675]



[1676]

Ethyl 3-{[(4-{[{5-[(5-cyanopyridin-2-yl)oxy]-3-methyl-1-benzofuran-2-yl}(cyclohexyl)methyl]amino}phenyl)carbonyl](methyl)amino}-propanoate (300 mg) obtained in Example A201 was dissolved in tetrahydrofuran (4.0 mL), and 1N aqueous sodium hydroxide solution (1.1 mL) was added to the solution, and the mixture was stirred at 50°C for 1 hr. The solvent was evaporated under reduced pressure, water (4 mL) was added to the residue, and the mixture was neutralized with 1N hydrochloric acid (1.1 mL) under ice-cooling and stirred at 0°C for 30 min. The resulting precipitate was collected by filtration, and dried to give the title compound (271 mg, 87%) as a colorless amorphous form.

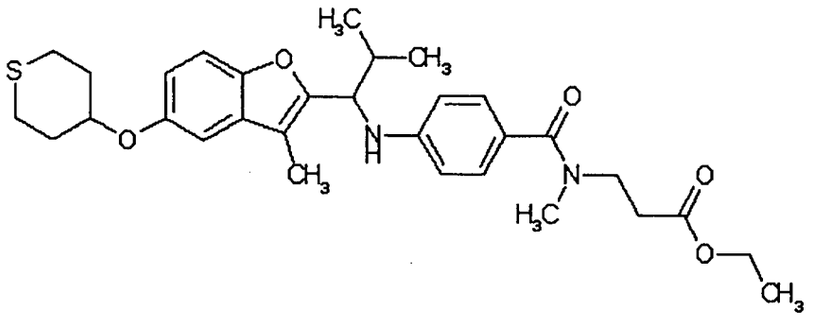
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.36 (m, 5 H), 1.52 - 2.11 (m, 7 H), 2.22 (s, 3 H), 2.61 (br. s., 2 H), 3.03 (s, 3 H), 3.66 (br. s., 2 H), 4.39 (d, J=7.9 Hz, 1 H), 6.56 (d, J=8.7 Hz, 2 H), 6.91 - 7.08 (m, 2 H), 7.12 - 7.25 (m, 3 H), 7.39 (d, J=8.7 Hz, 1 H), 7.90 (dd, J=8.7, 2.3 Hz, 1 H), 8.45 (d, J=2.3 Hz, 1 H).

[1677]

Example A203

ethyl 3-(methyl{[4-({2-methyl-1-[3-methyl-5-(tetrahydro-2H-thiopyran-4-yloxy)-1-benzofuran-2-yl]propyl}amino)phenyl]carbonyl}amino)propanoate

[1678]



[1679]

(1)1-(5-hydroxy-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-one

1-[5-(Benzyloxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-one (4.0 g) synthesized in Example A85(1) was dissolved in ethanol (80 mL), and palladium carbon-ethylenediamine complex (400 mg) was added to the solution at room temperature. The reaction mixture was stirred under hydrogen atmosphere (1 atm) at room temperature for 9.5 hr. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give the title compound (2.82 g, 100%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.24 (d, J=6.8 Hz, 6 H), 2.55 (s, 3 H), 3.48 - 3.63 (m, 1 H), 6.95 - 7.08 (m, 2 H), 7.32 - 7.40 (m, 1 H).

[1680]

(2)2-methyl-1-[3-methyl-5-(tetrahydro-2H-thiopyran-4-yloxy)-1-benzofuran-2-yl]propan-1-one

A solution of 1-(5-hydroxy-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-one (1.0 g) synthesized above, tetrahydro-2H-thiopyran-4-yl 4-methylbenzenesulfonate (2.99 g) and tripotassium phosphate (1.26 g) in N,N-dimethylformamide (10 mL) was stirred at 80°C for 3 hr then at 100°C for 14 hr. Tetrahydro-2H-thiopyran-4-yl 4-methylbenzenesulfonate (2.99 g) was added to the mixture, and the mixture was stirred at 100°C for 20 min. Tripotassium phosphate (600 mg) was added to the mixture, and the mixture was stirred at 100°C for 2 hr then at 120°C for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic

layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 90:10, v/v) to give the title compound (886 mg, 61%) as an orange oil. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.23 (d, J=6.8 Hz, 5 H), 1.82 - 2.29 (m, 4 H), 2.49 - 2.68 (m, 6 H), 2.88 - 3.00 (m, 2 H), 3.38 - 3.71 (m, 1 H), 4.25 - 4.50 (m, 1 H), 6.99 - 7.16 (m, 2 H), 7.40 (d, J=9.5 Hz, 1 H).

[1681]

(3)2-methyl-1-[3-methyl-5-(tetrahydro-2H-thiopyran-4-yloxy)-1-benzofuran-2-yl]propan-1-ol

2-Methyl-1-[3-methyl-5-(tetrahydro-2H-thiopyran-4-yloxy)-1-benzofuran-2-yl]propan-1-one (849 mg) synthesized above was dissolved in methanol (3 mL)-tetrahydrofuran (15 mL), and sodium tetrahydroborate (90%)(202 mg) was added to the solution at 0°C. The reaction mixture was stirred at 0°C for 30 min. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 85:15, v/v) to give the title compound (621 mg, 73%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.82 (d, J=6.8 Hz, 3 H), 1.12 (d, J=6.4 Hz, 3 H), 1.92 - 2.13 (m, 2 H), 2.16 - 2.27 (m, 6 H), 2.48 - 2.70 (m, 2 H), 2.89 - 3.01 (m, 2 H), 4.28 - 4.37 (m, 1 H), 4.46 (dd, J=8.3, 6.0 Hz, 1 H), 6.87 (dd, 1 H), 6.96 (d, J=2.6 Hz, 1 H), 7.30 (d, J=8.7 Hz, 1 H).

[1682]

(4) ethyl 3-(methyl{[4-({2-methyl-1-[3-methyl-5-(tetrahydro-2H-thiopyran-4-yloxy)-1-benzofuran-2-yl]propyl}amino)phenyl]carbonyl}amino)propanoate

To a solution of 2-methyl-1-[3-methyl-5-(tetrahydro-2H-thiopyran-4-yloxy)-1-benzofuran-2-yl]propan-1-ol (621 mg)

obtained above in tetrahydrofuran (5 mL) was added thionyl chloride (0.17 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 hr. To the reaction mixture was added aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give a colorless oil (648 mg). To the obtained colorless oil (648 mg) were added ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (509 mg) obtained in Example 2 (2), sodium iodide (581 mg), sodium carbonate (411 mg) and N,N-dimethylacetamide (5 mL), and the mixture was stirred at 80°C for 19 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 50:50, v/v) to give the title compound (495 mg, 46%) as a colorless oil.

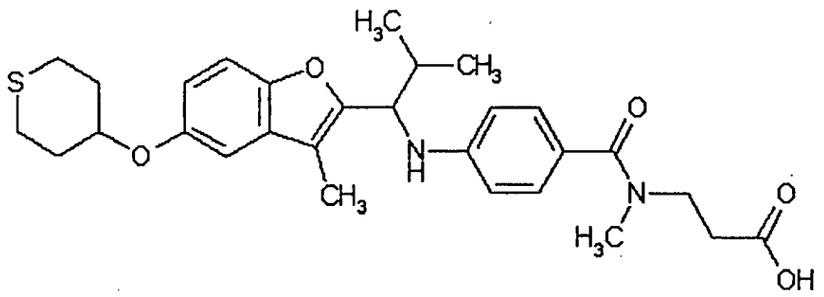
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.92 (d, J=6.8 Hz, 3 H), 1.13 (d, J=6.8 Hz, 3 H), 1.21 - 1.30 (m, 3 H), 1.95 - 2.09 (m, 2 H), 2.13 - 2.27 (m, 6 H), 2.49 - 2.67 (m, 4 H), 2.87 - 2.96 (m, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.2 Hz, 2 H), 4.07 - 4.16 (m, 2 H), 4.26 - 4.36 (m, 3 H), 6.57 (d, J=8.7 Hz, 2 H), 6.83 (dd, J=8.7, 2.6 Hz, 1 H), 6.91 (d, J=2.6 Hz, 1 H), 7.16 - 7.25 (m, 3 H).

[1683]

Example A204

3-(methyl{[4-({2-methyl-1-[3-methyl-5-(tetrahydro-2H-thiopyran-4-yloxy)-1-benzofuran-2-yl]propyl}amino)phenyl]carbonyl}amino)propanoic acid

[1684]



[1685]

Ethyl 3-(methyl{[4-({2-methyl-1-[3-methyl-5-(tetrahydro-2H-thiopyran-4-yloxy)-1-benzofuran-2-yl]propyl}amino)phenyl]carbonyl}amino)propanoate (485 mg) synthesized in Example A203 was dissolved in ethanol (2.0 mL) and tetrahydrofuran (2.0 mL), and 1N aqueous sodium hydroxide solution (1.96 mL) was added to the solution, and the mixture was stirred at room temperature for 0.5 hr. The solvent was evaporated under reduced pressure, water (4 mL) was added to the residue, and the mixture was neutralized with 1N hydrochloric acid (1.96 mL) under ice-cooling, and stirred for 30 min. The resulting precipitate was collected by filtration, and dried to give the title compound (421 mg, 91%) as a colorless amorphous form.

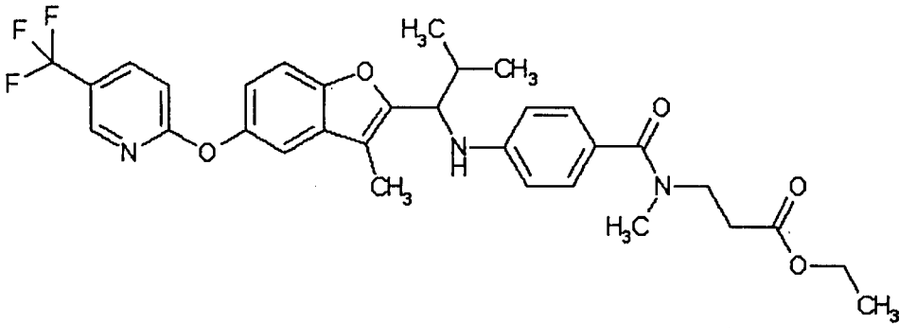
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (d, J=6.8 Hz, 3 H), 1.12 (d, J=6.8 Hz, 3 H), 1.96 - 2.07 (m, 2 H), 2.15 - 2.28 (m, 6 H), 2.48 - 2.71 (m, 5 H), 3.02 (s, 3 H), 3.62 - 3.75 (m, 2 H), 4.21 - 4.35 (m, 2 H), 4.55 - 4.73 (m, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.83 (dd, J=8.7, 2.7 Hz, 1 H), 6.91 (d, J=2.7 Hz, 1 H), 7.20 - 7.26 (m, 3 H).

[1686]

Example A205

ethyl 3-{methyl[(4-{[2-methyl-1-(3-methyl-5-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-1-benzofuran-2-yl)propyl]amino}phenyl)carbonyl]amino}propanoate

[1687]



[1688]

(1)2-methyl-1-(3-methyl-5-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-1-benzofuran-2-yl)propan-1-one

A solution of 1-(5-hydroxy-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-one (900 mg) synthesized in Example A203(1), 2-chloro-5-(trifluoromethyl)pyridine (898 mg) and potassium carbonate (854 mg) in N,N-dimethylformamide (5 mL) was stirred at 120°C for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 90:10, v/v) to give the title compound (1.23 g, 82%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.25 (d, J=6.8 Hz, 6 H), 2.58 (s, 3 H), 3.47 - 3.71 (m, 1 H), 7.06 (d, J=8.7 Hz, 1 H), 7.21 - 7.29 (m, 1 H), 7.42 (d, J=2.6 Hz, 1 H), 7.55 (d, J=8.7 Hz, 1 H), 7.92 (dd, J=8.7, 1.9 Hz, 1 H), 8.43 (s, 1 H).

[1689]

(2)2-methyl-1-(3-methyl-5-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-1-benzofuran-2-yl)propan-1-ol

2-Methyl-1-(3-methyl-5-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-1-benzofuran-2-yl)propan-1-one (1.22 g) synthesized above was dissolved in methanol (40 mL)-tetrahydrofuran (4 mL), and sodium tetrahydroborate (90%)(253 mg) was added to the solution at 0°C. The reaction mixture was stirred at 0°C for 2 hr. Water was added to the reaction mixture, and the mixture

was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give the title compound (1.22 g, 100%) as a colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.85 (d, 3 H), 1.13 (d, J=6.4 Hz, 3 H), 1.98 - 2.04 (m, 1 H), 2.15 - 2.30 (m, 4 H), 4.50 (dd, J=7.9, 3.8 Hz, 1 H), 6.94 - 7.09 (m, 2 H), 7.24 (d, J=2.3 Hz, 1 H), 7.45 (d, J=9.0 Hz, 1 H), 7.89 (dd, J=8.7, 2.3 Hz, 1 H), 8.45 (s, 1 H).

[1690]

(3) ethyl 3-{methyl[(4-{[2-methyl-1-(3-methyl-5-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-1-benzofuran-2-yl)propyl]amino}phenyl)carbonyl]amino}propanoate

To a solution of 2-methyl-1-(3-methyl-5-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-1-benzofuran-2-yl)propan-1-ol (776 mg) obtained above in tetrahydrofuran (5 mL) was added thionyl chloride (0.19 mL) at room temperature. The reaction mixture was stirred at room temperature for 3 hr. To the reaction mixture was added aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. To the obtained residue were added ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (557 mg) obtained in Example 2 (2), sodium iodide (636 mg), sodium carbonate (449 mg) and N,N-dimethylacetamide (5 mL), and the mixture was stirred at 80°C for 14 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 50:50, v/v) to give the title compound (436 mg, 34%) as a yellow amorphous compound.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 (d, J=6.4 Hz, 3 H), 1.15 (d,

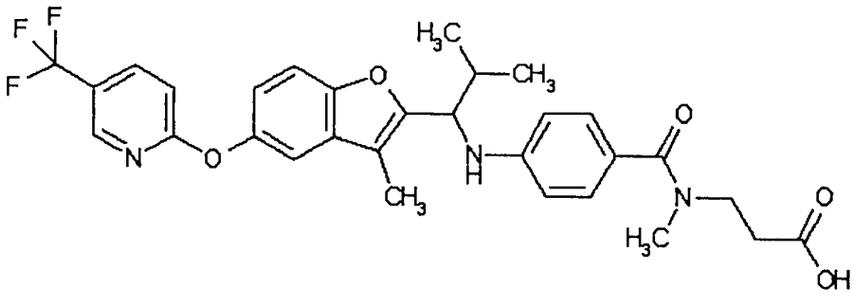
J=6.8 Hz, 3 H), 1.21 - 1.29 (m, 3 H), 1.60 (s, 3 H), 2.20 - 2.31 (m, 4 H), 2.62 (t, J=6.8 Hz, 2 H), 3.72 (t, J=7.2 Hz, 2 H), 4.12 (q, J=7.2 Hz, 2 H), 4.34 (d, 2 H), 6.58 (d, 2 H), 6.99 (td, J=5.8, 3.0 Hz, 2 H), 7.15 - 7.25 (m, 3 H), 7.39 (d, J=9.0 Hz, 1 H), 7.88 (dd, J=8.7, 2.3 Hz, 1 H), 8.43 (d, J=2.6 Hz, 1 H).

[1691]

Example A206

3-{methyl[(4-{[2-methyl-1-(3-methyl-5-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-1-benzofuran-2-yl)propyl]amino}phenyl)carbonyl]amino}propanoic acid

[1692]



[1693]

Ethyl 3-{methyl[(4-{[2-methyl-1-(3-methyl-5-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-1-benzofuran-2-yl)propyl]amino}phenyl)carbonyl]amino}propanoate (425 mg) synthesized in Example A205 was dissolved in tetrahydrofuran (4.0 mL), 1N aqueous sodium hydroxide solution (1.4 mL) was added to the solution, and the mixture was stirred at 50°C for 1.5 hr. The solvent was evaporated under reduced pressure, water (4 mL) was added to the residue, and the mixture was neutralized with 1N hydrochloric acid (1.4 mL) under ice-cooling and stirred for 20 min. The resulting precipitate was collected by filtration, and dried to give the title compound (378 mg, 94%) as a colorless amorphous form.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 (d, J=6.8 Hz, 3 H), 1.14 (d, J=6.4 Hz, 3 H), 2.16 - 2.30 (m, 4 H), 2.52 (br. s., 2 H), 2.99 (s, 3 H), 3.62 (br. s., 2 H), 4.34 (d, J=7.5 Hz, 1 H), 6.57 (d, J=8.7 Hz, 2 H), 6.89 - 7.05 (m, 2 H), 7.14 - 7.25 (m, 3 H),

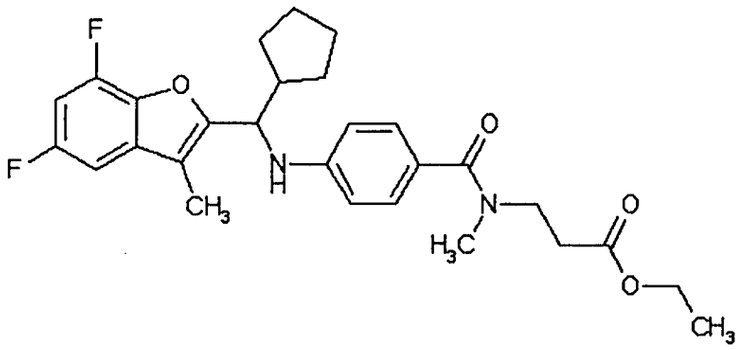
7.37 (d, J=9.0 Hz, 1 H), 7.89 (dd, J=8.9, 2.4 Hz, 1 H), 8.42 (s, 1 H).

[1694]

Example A207

ethyl 3-{[(4-{[cyclopentyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

[1695]



[1696]

(1) (2-acetyl-4,6-difluorophenoxy)acetic acid

A solution of 3',5'-difluoro-2'-hydroxyacetophenone (5.0 g), methyl bromoacetate (4.89 g) and potassium carbonate (6.01 g) in N,N-dimethylformamide (50 mL) was stirred at room temperature for 4 hr. The insoluble material was filtered off, 1N hydrochloric acid was added to the filtrate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a brown oil. To the obtained oil were added tetrahydrofuran (60 mL), ethanol (60 mL) and 1N aqueous sodium hydroxide solution (60 mL), and the mixture was stirred at room temperature for 30 min. The solvent was concentrated under reduced pressure, 1N hydrochloric acid (60 mL) was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title compound (6.67 g, 100%) as a pale-yellow solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.67 (s, 3 H), 4.81 (s, 2 H), 7.01 - 7.12 (m, 1 H), 7.20 - 7.26 (m, 1 H), 9.19 (br. s., 1 H).

[1697]

(2)5,7-difluoro-3-methyl-1-benzofuran

A mixture of (2-acetyl-4,6-difluorophenoxy)acetic acid (6.60 g) obtained above, sodium acetate (11.76 g) and acetic anhydride (40 mL) was stirred at 110°C for 8 hr. The reaction mixture was cooled to room temperature, water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution, saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (NH silica, hexane) to give the title compound (2.42 g, 50%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 2.21 (s, 3 H), 6.70 - 6.90 (m, 1 H), 6.97 (dd, J=8.0, 2.3 Hz, 1 H), 7.46 (s, 1 H).

[1698]

(3)cyclopentyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methanone

To a solution of 5,7-difluoro-3-methyl-1-benzofuran (1.0 g) synthesized above, and cyclopentanecarbonylchloride (867 mg) in nitromethane (20 mL) was added aluminum chloride (anhydrous) (1.19 g) at 0°C, and the mixture was stirred for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 95:5, v/v) to give the title compound (1.25 g, 80%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.62 - 2.16 (m, 8 H), 2.57 (s, 3 H), 3.66 - 3.85 (m, 1 H), 6.90 - 7.05 (m, 1 H), 7.10 (dd, J=7.3, 2.8 Hz, 1 H).

[1699]

(4)cyclopentyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methanol

Cyclopentyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methanone (1.24 g) synthesized above was dissolved in methanol (4 mL)-tetrahydrofuran (20 mL), and sodium tetrahydroborate (90%)(355 mg) was added to the solution at 0°C. The reaction mixture was stirred at 0°C for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give the title compound (1.18 g, 100%) as a yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 - 1.22 (m, 1 H), 1.43 - 1.75 (m, 6 H), 1.93 - 2.03 (m, 2 H), 2.22 (s, 3 H), 2.40 - 2.63 (m, 1 H), 4.56 (dd, J=9.0, 6.4 Hz, 1 H), 6.72 - 6.85 (m, 1 H), 6.87 - 6.95 (m, 1 H).

[1700]

(5) ethyl 3-{[(4-{[cyclopentyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a solution of cyclopentyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methanol (1.1 g) obtained above in tetrahydrofuran (10 mL) was added thionyl chloride (0.46 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 hr. Thionyl chloride (0.46 mL) was further added to the mixture, and the mixture was stirred at room temperature for 30 min. To the reaction mixture was added aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. To the obtained residue were added ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (1.09 g) obtained in Example 2 (2), sodium iodide (1.24 g), sodium carbonate (875 mg) and N,N-dimethylacetamide (10 mL), and the mixture was stirred at 80°C for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl

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acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 50:50, v/v) to give the title compound (252 mg, 12%) as a yellow amorphous compound.

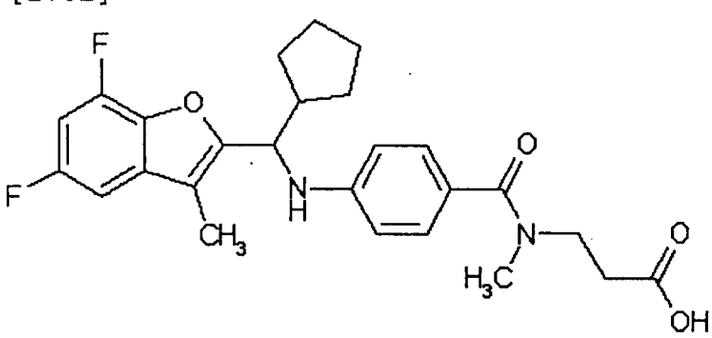
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.24 (dt, J=9.4, 7.1 Hz, 3 H), 1.46 - 1.79 (m, 7 H), 1.91 - 2.02 (m, 1 H), 2.25 (s, 3 H), 2.42 - 2.67 (m, 3 H), 3.01 (s, 3 H), 3.70 (t, J=7.2 Hz, 2 H), 4.04 - 4.16 (m, 2 H), 4.31 - 4.41 (m, 2 H), 6.56 (d, J=8.7 Hz, 2 H), 6.68 - 6.79 (m, 1 H), 6.88 (dd, J=8.0, 2.3 Hz, 1 H), 7.22 (d, J=8.3 Hz, 2 H).

[1701]

Example A208

3-{[(4-{[cyclopentyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1702]



[1703]

Ethyl 3-{[(4-{[cyclopentyl(5,7-difluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (240 mg) synthesized in Example A207 was dissolved in ethanol (1.0 mL)-tetrahydrofuran (1.0 mL), 1N aqueous sodium hydroxide solution (0.96 mL) was added to the solution, and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure, water (4 mL) was added to the residue, and the mixture was neutralized with 1N hydrochloric acid (0.96 mL) under ice-cooling, and stirred for 15 min. The resulting precipitate was collected by filtration,

and dried to give the title compound (185 mg, 82%) as a colorless amorphous form.

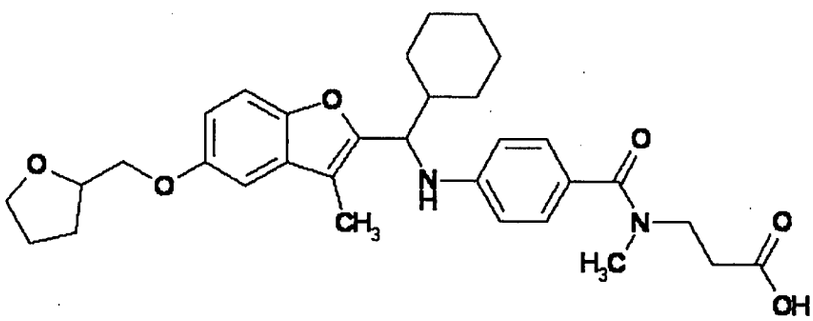
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.16 - 1.39 (m, 1 H), 1.43 - 1.75 (m, 7 H), 1.86 - 2.06 (m, 1 H), 2.24 (s, 3 H), 2.38 - 2.56 (m, 1 H), 2.66 (t, J=6.4 Hz, 2 H), 3.03 (s, 3 H), 3.70 (t, J=6.8 Hz, 2 H), 4.37 (d, J=9.4 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.68 - 6.80 (m, 1 H), 6.88 (dd, J=7.9, 2.3 Hz, 1 H), 7.24 (d, J=8.7 Hz, 2 H).

[1704]

Example A209

3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydrofuran-2-ylmethoxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

[1705]



[1706]

(1)cyclohexyl[3-methyl-5-(tetrahydrofuran-2-ylmethoxy)-1-benzofuran-2-yl]methanone

A solution of 1-(5-hydroxy-3-methyl-1-benzofuran-2-yl)-2-methylpropan-1-one (300 mg) synthesized in Example A203(1), tetrahydrofurfuryl bromide (230 mg), potassium carbonate (240 mg) in N,N-dimethylformamide (3 mL) was stirred at 80°C for 2 hr then at 120°C for 4 hr. Tetrahydrofurfuryl bromide (230 mg) was added to the mixture, and the mixture was stirred at 120°C for 60 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column

chromatography (hexane-ethyl acetate 100:0 - 90:10, v/v) to give the title compound (275 mg, 69%) as a colorless oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.20 - 1.51 (m, 5 H), 1.68 - 2.17 (m, 9 H), 2.56 (s, 3 H), 3.20 - 3.39 (m, 1 H), 3.76 - 3.98 (m, 2 H), 4.02 (d, J=5.3 Hz, 2 H), 4.24 - 4.37 (m, 1 H), 7.03 (d, J=2.6 Hz, 1 H), 7.13 (dd, J=9.0, 2.6 Hz, 1 H), 7.39 (d, J=8.7 Hz, 1 H).

[1707]

(2)cyclohexyl[3-methyl-5-(tetrahydrofuran-2-ylmethoxy)-1-benzofuran-2-yl]methanol

Cyclohexyl[3-methyl-5-(tetrahydrofuran-2-ylmethoxy)-1-benzofuran-2-yl]methanone (260 mg) synthesized above was dissolved in methanol (0.5 mL)-tetrahydrofuran (2.5 mL), and sodium tetrahydroborate (90%)(64 mg) was added to the solution at 0°C. The reaction mixture was stirred at 0°C for 2.5 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give the title compound (235 mg, 90%) as a colorless oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.77 - 1.46 (m, 8 H), 1.61 - 1.69 (m, 2 H), 1.72 - 2.01 (m, 6 H), 2.18 (s, 3 H), 3.78 - 3.89 (m, 1 H), 3.92 - 4.05 (m, 3 H), 4.22 - 4.39 (m, 1 H), 4.50 (d, J=8.7 Hz, 1 H), 6.87 - 6.92 (m, 1 H), 6.94 (d, J=2.6 Hz, 1 H), 7.29 (d, J=9.1 Hz, 1 H).

[1708]

(3)3-[{[4-({cyclohexyl[3-methyl-5-(tetrahydrofuran-2-ylmethoxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid

To a solution of cyclohexyl[3-methyl-5-(tetrahydrofuran-2-ylmethoxy)-1-benzofuran-2-yl]methanol (220 mg) obtained above in tetrahydrofuran (2 mL) was added thionyl chloride (70 μL) at room temperature. The reaction mixture was stirred at room temperature for 2 hr. To the reaction mixture was added aqueous sodium hydrogen carbonate solution, and the mixture

was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. To the obtained residue were added ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (168 mg) obtained in Example 2 (2), sodium iodide (192 mg), sodium carbonate (136 mg) and N,N-dimethylacetamide (3.0 mL), and the mixture was stirred at 80°C for 14 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 0:100, v/v) to give a colorless amorphous form (120 mg). The obtained colorless amorphous form (120 mg) was dissolved in ethanol (1.0 mL)-tetrahydrofuran (1.0 mL), 1N aqueous sodium hydroxide solution (0.44 mL) was added to the solution, and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure, water (1 mL) was added to the residue, and the mixture was neutralized with 1N hydrochloric acid (0.44 mL) under ice-cooling and stirred for 10 min. The resulting precipitate was collected by filtration, and dried to give the title compound (97 mg, 80%) as a colorless solid.

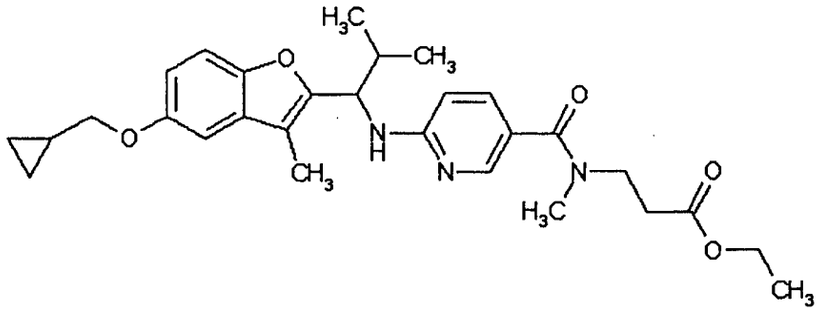
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.93 - 1.29 (m, 5 H), 1.47 - 2.14 (m, 11 H), 2.20 (s, 3 H), 2.54 - 2.72 (m, 2 H), 3.02 (s, 3 H), 3.67 (t, J=6.4 Hz, 2 H), 3.77 - 3.90 (m, 1 H), 3.91 - 4.03 (m, 3 H), 4.19 - 4.32 (m, 1 H), 4.35 (d, J=7.9 Hz, 1 H), 6.55 (d, J=8.7 Hz, 2 H), 6.79 - 6.95 (m, 2 H), 7.16 - 7.25 (m, 3 H).

[1709]

Example A210

ethyl 3-[{[6-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridin-3-yl]carbonyl}(methyl)amino]propanoate

[1710]



[1711]

(1) methyl 6-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridine-3-carboxylate

To a solution of 1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-ol (1.41 g) obtained in Example A75(3) in tetrahydrofuran (10 mL) was added thionyl chloride (0.45 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 hr. To the reaction mixture was added aqueous sodium hydrogen carbonate solution ice-cooled to 0°C, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give a colorless solid (1.42 g). To the obtained colorless solid (710 mg) were added methyl 6-aminopyridine-3-carboxylate (411 mg), sodium iodide (770 mg), sodium carbonate (545 mg) and N,N-dimethylacetamide (6 mL), and the mixture was stirred at 80°C for 22 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 50:50, v/v) to give the title compound (265 mg, 25%) as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.33 - 0.39 (m, 2 H), 0.60 - 0.69 (m, 2 H), 0.88 - 0.95 (m, 3 H), 1.10 (d, J=6.8 Hz, 3 H), 2.94 (s, 3 H), 3.01 (s, 3 H), 3.82 - 3.88 (m, 4 H), 5.01 (t, 1 H), 5.40 (d, J=8.7 Hz, 1 H), 6.34 (d, J=8.3 Hz, 1 H), 6.85 - 6.95 (m, 2 H), 7.21 - 7.27 (m, 1 H), 7.91 (dd, J=9.0, 2.3 Hz, 1 H),

8.74 (d, J=1.9 Hz, 1 H).

[1712]

(2) 6-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridine-3-carboxylic acid

To a mixture of methyl 6-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridine-3-carboxylate (260 mg) obtained above, tetrahydrofuran (1.2 mL) and ethanol (1.2 mL) was added 1N aqueous sodium hydroxide solution (1.2 mL), and the mixture was stirred with heating under reflux for 5 hr. 1N Aqueous sodium hydroxide solution (1.2 mL) was added to the mixture, and the mixture was stirred with heating under reflux for 16 hr. 8N Aqueous sodium hydroxide solution (1.2 mL) was added to the mixture, and the mixture was further stirred with heating under reflux for 1 hr. The reaction mixture was concentrated under reduced pressure, water (4 mL) was added to the residue, and 1N hydrochloric acid (10.8 mL) was added to the mixture under ice-cooling, and the mixture was stirred for 10 min. The resulting precipitate was collected by filtration, and dried to give the title compound (145 mg, 58%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.31 - 0.37 (m, 2 H), 0.61 - 0.66 (m, 2 H), 0.94 (d, J=6.8 Hz, 3 H), 1.15 (d, J=6.8 Hz, 3 H), 1.21 - 1.37 (m, 1 H), 2.22 (s, 3 H), 2.31 - 2.48 (m, 1 H), 3.82 (d, J=6.8 Hz, 2 H), 4.66 (br. s., 1 H), 6.36 (d, J=8.7 Hz, 1 H), 6.79 - 6.92 (m, 2 H), 7.22 - 7.29 (m, 1 H), 8.05 (dd, J=9.1, 1.9 Hz, 1 H), 8.75 (d, J=1.9 Hz, 1 H).

[1713]

(3) ethyl 3-[{[6-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridin-3-yl]carbonyl}(methyl)amino]propanoate

A mixture of 6-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridine-3-carboxylic acid (145 mg) synthesized above, ethyl 3-(methylamino)propanoate (58 mg), 1-hydroxybenzotriazole·monohydrate (67 mg), triethylamine (122 µL), 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide hydrochloride (84 mg) and N,N-dimethylformamide (2 mL) was stirred at room temperature for 18 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 100:0 - 0:100, v/v) to give the title compound (104 mg, 56%) as a colorless amorphous form.

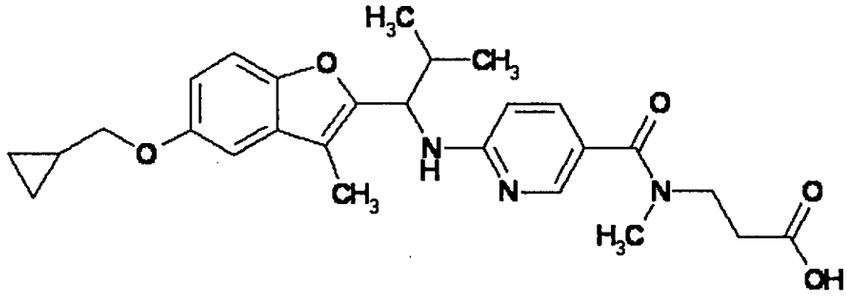
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.26 - 0.49 (m, 2 H), 0.58 - 0.70 (m, 2 H), 0.86 - 1.00 (m, 3 H), 1.04 - 1.15 (m, 3 H), 1.18 - 1.31 (m, 4 H), 2.18 - 2.30 (m, 4 H), 2.63 (t, J=6.8 Hz, 2 H), 3.06 (s, 3 H), 3.73 (t, J=7.0 Hz, 2 H), 3.82 (d, J=6.8 Hz, 2 H), 4.13 (q, J=7.2 Hz, 2 H), 4.94 (t, J=8.5 Hz, 1 H), 5.18 (d, J=8.7 Hz, 1 H), 6.34 (d, J=8.3 Hz, 1 H), 6.79 - 6.91 (m, 2 H), 7.22 - 7.26 (m, 1 H), 7.47 (dd, J=8.3, 2.3 Hz, 1 H).

[1714]

Example A211

3-[{[6-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridin-3-yl]carbonyl}(methyl)amino]propanoic acid

[1715]



[1716]

Ethyl 3-[{[6-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridin-3-yl]carbonyl}(methyl)amino]propanoate (100 mg) synthesized in Example A210 was dissolved in ethanol (0.5 mL)-tetrahydrofuran (0.5 mL), 1N aqueous sodium hydroxide solution (0.4 mL) was

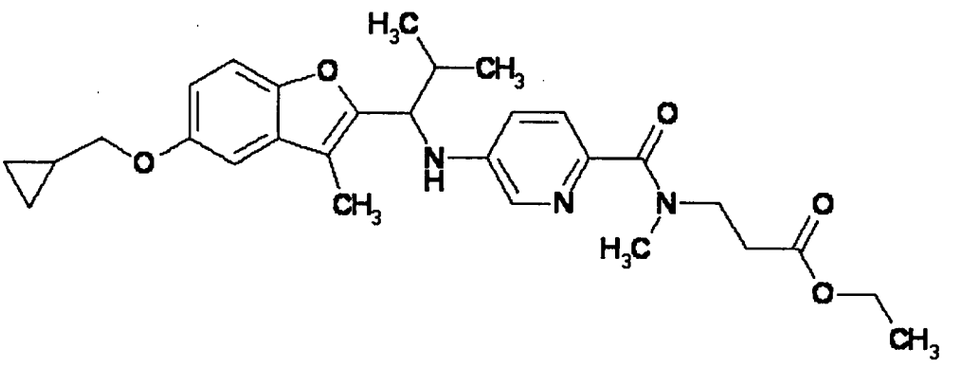
added to the solution, and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure, water (0.5 mL) was added to the residue, and the mixture was neutralized with 1N hydrochloric acid (0.4 mL) under ice-cooling, and the mixture was stirred for 20 min. The resulting precipitate was collected by filtration, and dried to give the title compound (77 mg, 80%) as a colorless solid. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.30 - 0.43 (m, 2 H), 0.57 - 0.69 (m, 2 H), 0.92 (d, J=6.4 Hz, 3 H), 1.15 (d, J=6.4 Hz, 3 H), 1.23 - 1.35 (m, 1 H), 2.21 (s, 3 H), 2.30 - 2.43 (m, 1 H), 2.66 (t, J=6.2 Hz, 2 H), 3.06 (s, 3 H), 3.70 - 3.77 (m, 2 H), 3.82 (d, J=7.2 Hz, 2 H), 4.43 (br. s., 1 H), 6.38 (d, J=9.1 Hz, 1 H), 6.80 - 6.91 (m, 2 H), 7.26 - 7.30 (m, 1 H), 7.57 (dd, J=8.7, 1.9 Hz, 1 H), 8.10 (br. s., 1 H).

[1717]

Example A212

ethyl 3-[{[5-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridin-2-yl]carbonyl}(methyl)amino]propanoate

[1718]



[1719]

(1) methyl 5-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridine-2-carboxylate

To a solution of 1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropan-1-ol (1.41 g) obtained in Example A75(3) in tetrahydrofuran (10 mL) was added thionyl chloride (0.45 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 hr. To the reaction

mixture was added aqueous sodium hydrogen carbonate solution ice-cooled to 0°C, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give a colorless solid (1.42 g). To the obtained colorless solid (710 mg) were added methyl 5-aminopyridine-2-carboxylate (411 mg), sodium iodide (770 mg), sodium carbonate (545 mg) and N,N-dimethylacetamide (6 mL), and the mixture was stirred at 80°C for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 50:50, v/v) to give the title compound (424 mg, 40%) as a brown oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.29 - 0.40 (m, 2 H), 0.60 - 0.69 (m, 2 H), 0.93 (d, J=6.8 Hz, 3 H), 1.14 (d, J=6.8 Hz, 3 H), 2.20 - 2.31 (m, 4 H), 3.82 (d, J=6.8 Hz, 2 H), 3.91 (s, 3 H), 4.34 (t, J=8.0 Hz, 1 H), 4.65 (d, J=8.3 Hz, 1 H), 6.81 - 6.91 (m, 3 H), 7.23 (d, J=9.5 Hz, 1 H), 7.89 (d, J=8.3 Hz, 1 H), 8.10 (d, J=2.7 Hz, 1 H).

[1720]

(2)5-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridine-2-carboxylic acid

To a mixture of methyl 5-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridine-2-carboxylate (410 mg) synthesized above, tetrahydrofuran (2.0 mL) and ethanol (2.0 mL) was added 1N aqueous sodium hydroxide solution (2.0 mL), and the mixture was stirred with heating under reflux for 14 hr. The reaction mixture was concentrated under reduced pressure, water (4 mL) was added to the residue, 1N hydrochloric acid (2 mL) was added under ice-cooling, and the mixture was stirred for 20 min. The resulting precipitate was collected by filtration, and dried to give the title

compound (323 mg, 80%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.35 (q, 2 H), 0.60 - 0.68 (m, 2 H), 0.94 (d, J=6.8 Hz, 3 H), 1.15 (d, J=6.8 Hz, 3 H), 1.24 - 1.35 (m, 1 H), 2.18 - 2.38 (m, 4 H), 3.82 (d, J=7.2 Hz, 2 H), 4.35 (br. s., 1 H), 4.98 (br. s., 1 H), 6.82 - 6.90 (m, 2 H), 6.96 (dd, J=8.7, 2.6 Hz, 1 H), 7.20 - 7.28 (m, 1 H), 7.95 (d, J=8.7 Hz, 1 H), 8.08 (br. s., 1 H).

[1721]

(3) ethyl 3-[{[5-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridin-2-yl]carbonyl}(methyl)amino]propanoate

A mixture of 5-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridine-2-carboxylic acid (311 mg) synthesized above, ethyl 3-(methylamino)propanoate (131 mg), 1-hydroxybenzotriazole·monohydrate (145 mg), triethylamine (265 µL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (182 mg) and N,N-dimethylformamide (2 mL) was stirred at room temperature for 16 hr. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 100:0 - 0:100, v/v) to give the title compound (291 mg, 73%) as a colorless amorphous form.

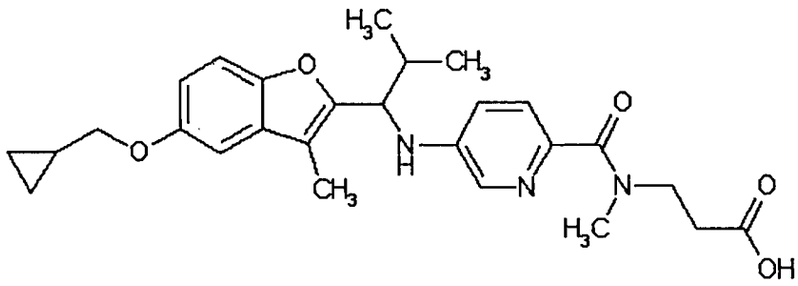
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.31 - 0.39 (m, 2 H), 0.64 (q, J=6.1 Hz, 2 H), 0.92 (d, J=6.8 Hz, 3 H), 1.14 (d, 3 H), 1.22 - 1.31 (m, 3 H), 1.63 (s, 3 H), 2.17 - 2.30 (m, 4 H), 2.62 - 2.75 (m, 2 H), 3.71 - 3.93 (m, 4 H), 4.01 - 4.18 (m, 3 H), 4.24 - 4.36 (m, 1 H), 4.40 - 4.47 (m, 1 H), 6.75 - 6.92 (m, 3 H), 7.20 - 7.25 (m, 1 H), 7.53 (br. s., 1 H), 7.93 (br. s., 1 H).

[1722]

Example A213

3-[{[5-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridin-2-yl]carbonyl}(methyl)amino]propanoic acid

[1723]



[1724]

Ethyl 3-[{[5-({1-[5-(cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)pyridin-2-yl]carbonyl}(methyl)amino]propanoate (280 mg) synthesized in Example A212 was dissolved in ethanol (1.0 mL)-tetrahydrofuran (1.0 mL), 1N aqueous sodium hydroxide solution (1.1 mL) was added to the solution, and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure, water (2.0 mL) was added to the residue, and the mixture was neutralized with 1N hydrochloric acid (1.1 mL) under ice-cooling, and stirred for 30 min. The resulting precipitate was collected by filtration, and dried to give the title compound (238 mg, 90%) as a colorless solid.

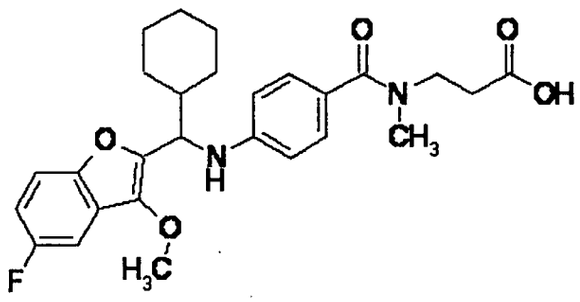
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.28 - 0.41 (m, 2 H), 0.57 - 0.68 (m, 2 H), 0.91 (d, J=6.4 Hz, 3 H), 1.12 (d, J=6.4 Hz, 3 H), 2.18 - 2.31 (m, 4 H), 2.77 (br. s., 2 H), 3.06 (br. s., 3 H), 3.68 - 3.77 (m, 2 H), 3.80 - 3.85 (m, 2 H), 4.29 (d, J=7.6 Hz, 2 H), 4.66 (br. s., 1 H), 6.80 - 7.00 (m, 3 H), 7.24 (d, J=8.7 Hz, 1 H), 7.61 (br. s., 1 H), 7.93 (br. s., 1 H).

[1725]

Example A214

3-{[(4-{[cyclohexyl(5-fluoro-3-methoxy-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1726]



[1727]

(1) cyclohexyl(5-fluoro-3-hydroxy-1-benzofuran-2-yl)methanone

1-(5-Fluoro-2-hydroxyphenyl)ethanone (4.0 g) was dissolved in acetonitrile (80 mL). To the reaction mixture were added potassium carbonate (4.8 g) and 2-bromo-1-cyclohexylethanone (7.3 g) synthesized in Example A51(1) at room temperature, and the mixture was stirred at room temperature for 8 hr. The reaction mixture was filtered through celite, rinsed with ethyl acetate, and the filtrate was concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (50 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (5.3 mL) was added to the solution, and the mixture was stirred with heating at 110°C for 1 hr. After cooling to room temperature, the reaction mixture was quenched with 1N hydrochloric acid, and the mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure, and the precipitated compound was recrystallized from diisopropyl ether-ethanol to give the title object compound (4.7 g, 76%) as a colorless solid.
$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.03 - 2.12 (m, 10 H), 3.00 - 3.26 (m, 1 H), 5.24 (s, 1 H), 7.14 - 7.50 (m, 3 H).

[1728]

(2) cyclohexyl(5-fluoro-3-methoxy-1-benzofuran-2-yl)methanone

Cyclohexyl(5-fluoro-3-hydroxy-1-benzofuran-2-yl)methanone (3.0 g) synthesized in the above-mentioned (1) was dissolved in tetrahydrofuran (15 mL) and N,N-dimethylformamide (15 mL). The reaction mixture was ice-cooled, sodium hydride (0.69 mg) was added to the solution, and the mixture was stirred for 15

min. Dimethyl sulfate (1.6 mL) was added to the mixture, and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the precipitate was recrystallized from diisopropyl ether-hexane to give the title object compound (2.0 g, 63%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.16 - 2.03 (m, 10 H), 3.23 (tt, J=11.2, 3.1 Hz, 1 H), 4.26 (s, 3 H), 7.20 - 7.54 (m, 3 H).

[1729]

(3) cyclohexyl(5-fluoro-3-methoxy-1-benzofuran-2-yl)methanol

Cyclohexyl(5-fluoro-3-methoxy-1-benzofuran-2-yl)methanone (2.0 g) synthesized in the above-mentioned (2) was dissolved in tetrahydrofuran (15 mL) and methanol (3 mL), and sodium borohydride (90%, 0.59 g) was added to the solution under ice-cooling. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 hr then ice-cooled again, and water (2 mL) and 1N hydrochloric acid (10 mL) were carefully added to the mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a crude product (1.9 g, quantitative) of the title object compound as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.86 - 2.19 (m, 12 H), 3.97 (s, 3 H), 4.61 (d, J=8.3 Hz, 1 H), 6.98 - 7.33 (m, 3 H).

[1730]

(4) ethyl 3-{[(4-{[cyclohexyl(5-fluoro-3-methoxy-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a solution (15 mL) of cyclohexyl(5-fluoro-3-methoxy-1-benzofuran-2-yl)methanol (1.9 g) synthesized in the above-mentioned (3) in tetrahydrofuran was added thionyl chloride (0.48 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min then ice-cooled, and saturated aqueous sodium hydrogen carbonate solution (15 mL)

was carefully added to the mixture. The reaction mixture was stirred for 10 min, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in dimethylacetamide (15 mL), sodium iodide (0.98 g), sodium carbonate (0.65 g) and ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (0.90 g) synthesized in Example 2(2) were added to the solution, and the mixture was stirred at 70°C for 4 hr. After allowing to cool, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:1, volume ratio) to give the title object compound (0.30 g, 16%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 - 2.19 (m, 14 H), 2.61 (t, J=7.2 Hz, 2 H), 3.01 (s, 3 H), 3.70 (t, J=7.2 Hz, 2 H), 3.94 (s, 3 H), 4.11 (q, J=7.2 Hz, 2 H), 4.30 - 4.46 (m, 2 H), 6.63 (d, J=8.7 Hz, 2 H), 6.93 - 7.25 (m, 5 H).

[1731]

(5)3-{[(4-{[cyclohexyl(5-fluoro-3-methoxy-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

Ethyl 3-{[(4-{[cyclohexyl(5-fluoro-3-methoxy-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (0.30 g) synthesized in the above-mentioned (4) was dissolved in ethanol (5 mL), 1N aqueous sodium hydroxide solution (1.0 mL) was added to the solution at room temperature, and the mixture was stirred at room temperature for 0.5 hr. Ethanol was evaporated under reduced pressure, and 1N hydrochloric acid (1.0 mL) was added to the residue. The precipitate was washed with water to give the title object compound (0.15 g, 52%) as a colorless solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.94 - 2.20 (m, 11 H), 2.70 (t, J=6.4 Hz, 2 H), 3.05 (s, 3 H), 3.71 (t, J=6.4 Hz, 2 H), 3.94

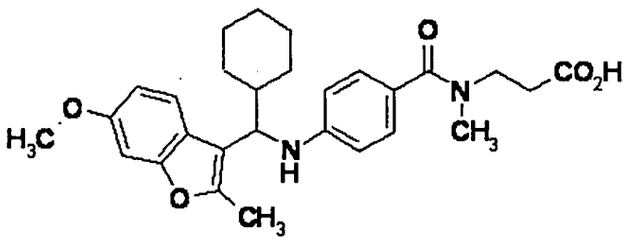
(s, 3 H), 4.46 (d, J=8.3 Hz, 1 H), 6.64 (d, J=9.0 Hz, 2 H), 6.94 (td, J=9.0, 2.6 Hz, 1 H), 7.14 - 7.31 (m, 4 H).

[1732]

Example A215

3-{[(4-{[cyclohexyl(6-methoxy-2-methyl-1-benzofuran-3-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

[1733]



[1734]

(1)cyclohexyl(6-methoxy-2-methyl-1-benzofuran-3-yl)methanone

To a mixture of 6-methoxy-2-methyl-1-benzofuran (1.50 g), cyclohexanecarbonyl chloride (1.36 mL) and nitromethane (15 mL) was added aluminum chloride (1.85 g) at 0°C, and the mixture was stirred for 1 hr. Water was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 10% ethyl acetate/hexane) to give the title object compound (1.18 g, 47%) as a yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 1.20 - 1.62 (m, 5 H), 1.69 - 1.81 (m, 1 H), 1.82 - 2.02 (m, 4 H), 2.73 (s, 3 H), 2.95 - 3.09 (m, 1 H), 3.85 (s, 3 H), 6.93 (dd, J=8.7, 2.2 Hz, 1 H), 6.97 (d, J=2.2 Hz, 1 H), 7.68 (d, J=8.7 Hz, 1 H).

[1735]

(2)cyclohexyl(6-methoxy-2-methyl-1-benzofuran-3-yl)methanol

To a mixture of cyclohexyl(6-methoxy-2-methyl-1-benzofuran-3-yl)methanone (1.18 g) synthesized above, methanol (1 mL) and tetrahydrofuran (10 mL) was added sodium borohydride (246 mg) at 0°C, and the mixture was stirred for 30

min. 1N Hydrochloric acid was added to quench the reaction, the organic solvent was evaporated in an evaporator, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (906 mg, 76%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.76 - 0.97 (m, 1 H), 0.99 - 1.38 (m, 4 H), 1.37 - 1.50 (m, 1 H), 1.51 - 1.72 (m, 2 H), 1.74 - 2.00 (m, 2 H), 2.11 - 2.24 (m, 1 H), 2.38 (s, 3 H), 3.83 (s, 3 H), 4.50 (d, J=8.0 Hz, 1 H), 6.81 (dd, J=8.5, 2.2 Hz, 1 H), 6.93 (d, J=2.2 Hz, 1 H), 7.51 (d, J=8.5 Hz, 1 H).

[1736]

(3) 3-[chloro(cyclohexyl)methyl]-6-methoxy-2-methyl-1-benzofuran

To a solution (10 mL) of cyclohexyl(6-methoxy-2-methyl-1-benzofuran-3-yl)methanol (499 mg) synthesized above in toluene was added thionyl chloride (159 μL), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into ice-cooled saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title object compound (530 mg, 99%) as a pale-yellow oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.72 - 0.92 (m, 1 H), 0.97 - 1.40 (m, 4 H), 1.44 - 1.72 (m, 3 H), 1.76 - 1.89 (m, 1 H), 2.05 - 2.22 (m, 1 H), 2.29 - 2.46 (m, 4 H), 3.83 (s, 3 H), 4.74 (d, J=9.3 Hz, 1 H), 6.84 (dd, J=8.5, 2.4 Hz, 1 H), 6.93 (d, J=2.4 Hz, 1 H), 7.55 (d, J=8.5 Hz, 1 H).

[1737]

(4) ethyl 3-{[(4-{[cyclohexyl(6-methoxy-2-methyl-1-benzofuran-3-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate

To a mixture of 3-[chloro(cyclohexyl)methyl]-6-methoxy-2-methyl-1-benzofuran (530 mg) synthesized above, ethyl 3-{[(4-aminophenyl)carbonyl](methyl)amino}propanoate (498 mg)

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synthesized in Example 2(2) and N,N-dimethylformamide (10 mL) were added sodium iodide (408 mg) and sodium carbonate (288 mg), and the mixture was stirred at 80°C overnight. Saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 - 70% ethyl acetate/hexane) to give the title object compound (781 mg, 85%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 - 1.37 (m, 8 H), 1.54 - 1.96 (m, 5 H), 1.99 - 2.12 (m, 1 H), 2.42 (s, 3 H), 2.60 (t, J=6.9 Hz, 2 H), 3.00 (s, 3 H), 3.69 (t, J=6.9 Hz, 2 H), 3.82 (s, 3 H), 4.11 (q, J=7.1 Hz, 2 H), 4.19 - 4.32 (m, 2 H), 6.47 (d, J=8.5 Hz, 2 H), 6.79 (dd, J=8.5, 2.2 Hz, 1 H), 6.91 (d, J=2.2 Hz, 1 H), 7.17 (d, J=8.5 Hz, 2 H), 7.40 (d, J=8.5 Hz, 1 H).

[1738]

(5)3-{[(4-{[cyclohexyl(6-methoxy-2-methyl-1-benzofuran-3-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid

To a mixture of ethyl 3-{[(4-{[cyclohexyl(6-methoxy-2-methyl-1-benzofuran-3-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoate (781 mg) synthesized above, tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The residue was dissolved in water (10 mL), and 1N hydrochloric acid (2.00 mL) was added at 0°C. The resulting precipitate was collected by filtration to give the title object compound (702 mg, 95%) as a white solid.

$^1$H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 - 1.36 (m, 5 H), 1.57 - 1.97 (m, 5 H), 1.99 - 2.11 (m, 1 H), 2.41 (s, 3 H), 2.64 (t, J=6.6 Hz, 2 H), 3.01 (s, 3 H), 3.68 (t, J=6.6 Hz, 2 H), 3.81 (s, 3 H), 4.24 (d, J=7.5 Hz, 1 H), 6.47 (d, J=8.7 Hz, 2 H), 6.79 (dd, J=8.7, 2.3 Hz, 1 H), 6.91 (d, J=2.3 Hz, 1 H), 7.18 (d, J=8.7

781

Hz, 2 H), 7.40 (d, J=8.7 Hz, 1 H).

[1739]

Experimental Example 1

The glucagon binding inhibitory action of the compound of the present invention was evaluated by the following method.

(1) cloning of human glucagon receptor gene

Human glucagon receptor gene was cloned by PCR reaction using human pancreas Marathon-ready cDNA (Clontech) as a template and the following primer set.

GGR-U:

5'-AATAGAATTCATGCCCCCCTGCCAGCCACAG-3' (SEQ ID NO: 1)

GGR-L:

5'-CTAAGCGGCCGCTCAGAAGGGGCTCTCAGCCAATCT-3' (SEQ ID NO: 2)

PCR reaction was performed using Advantage 2 polymerase (Clontech) and according to the attached protocol. The obtained PCR product was electrophoresed on an agarose gel (1%). An about 1.4 kb of DNA fragment containing a glucagon receptor gene was recovered from the gel and digested with restriction enzymes EcoRI and NotI. DNA treated with the restriction enzymes was electrophoresed on an agarose gel (1%). An about 1.4 kb of DNA fragment was recovered and ligated to plasmid pMSRαneo digested with restriction enzymes EcoRI and NotI to construct a human-type glucagon receptor expression plasmid DNA "pMSRαneo/hGCGR". The base sequence of an inserted fragment was confirmed and the base sequence was confirmed to be in consistency with that of the object sequence.

[1740]

(2) preparation of glucagon receptor membrane protein

A human-type glucagon receptor was expressed using FreeStyle CHO Expression System (Invitrogen). A transient expression in FreeStyle CHO cell was performed using a human-type glucagon receptor expression plasmid DNA "pMSRαneo/hGCGR" and according to the manual attached to the FreeStyle CHO Expression System. The above-mentioned DNA was transfected and the cultured with shaking for 2 days (37°C, 8% $CO_2$, 125 rpm).

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2400 ml of culture medium was centrifuged at 2,000 rpm for 10 min and the cells were collected. The collected cells were washed with PBS, suspended in homogenate buffer [10 mM $NaHCO_3$ (pH 7.4), 1 mM EDTA, Complete EDTA-free (Roche, 1 tablet/50 ml)] and disrupted by polytron cell disrupter (Kinematica AG). Disruption solution was centrifuged at 2,000 rpm for 10 min and the supernatant was collected. The supernatant was centrifuged at 35,000 rpm for 60 min and the precipitate was suspended in a buffer [20 mM Tris-HCl (pH 7.4), 5 mM EDTA, Complete EDTA-free (Roche, 1 tablet/50 ml)] to give a glucagon receptor membrane protein (452 mg).

[1741]

(3) measurement of glucagon binding inhibitory activity

To each well of 96 well plate (Corning Incorporated) were added 25 µl of test compound (containing 0.4% DMSO), 50 µl of glucagon receptor membrane protein diluted with reaction buffer [50 mM Tris-HCl (pH 7.4), 5 mM EGTA, 5 mM magnesium chloride, 0.1% BSA, 0.005% Tween20] to 100 µg/ml, and 25 µl of radioactive labeled glucagon ([$^{125}$I]-Receptor Grade Glucagon; Perkin Elmer Inc.) diluted with the reaction buffer to 200 pM, whereby the reaction was started. The plate was stood for 90 min at room temperature. The reaction solution was transferred from the reaction plate to a 96 well unifilter GF/C plate (Perkin Elmer Inc.) using a cell harvester (Perkin Elmer Inc.) and the membrane fraction was collected on the filter by suction. The filter was presoaked in 2 mg/ml of polyethyleneimine to prevent non-specific adsorption of labeled ligand. The filter was washed 4 times with a reaction buffer and dried for 2 hr at 42°C. To each well was added 25 µl of scintillator (MicroScint0; Perkin Elmer Inc.), and the fluorescence amount was measured using a microplate scintillation counter (TopCount NXT™; Perkin Elmer Inc.). The glucagon binding inhibitory activity ($IC_{50}$ value) of the well added with the test compound (containing 0.4% DMSO) was calculated, using the reaction rate of the well added only

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with 0.4% DMSO as 0% inhibitory rate, and the reaction rate of the well added with non-labeled glucagon (final concentration 1 μM) as 100% inhibitory rate. The results are shown in Table 1.

[1742]

Table 1

| test compound | $IC_{50}$ value (nM) |
|---|---|
| Example 8 | 410 |
| Example 41 | 2300 |
| Example 61 | 320 |
| Example A3 | 1700 |
| Example A7 | 1800 |
| Example A12 | 210 |
| Example A17 | 230 |
| Example A49 | 640 |
| Example A53 | 570 |
| Example A73 | 900 |
| Example A78 | 280 |
| Example A83 | 84 |

[1743]

In addition, the inhibitory rate (%) of the well added with the test compound (10 μM; containing 0.4% DMSO) was calculated, using the reaction rate of the well added only with 0.4% DMSO as 0% inhibitory rate, and the reaction rate of the well added with non-labeled glucagon (final concentration 1 μM) as 100% inhibitory rate. The results are shown in Table 2.

[1744]

[Table 2-1]

Table 2

| test compound | inhibitory rate (%) at 10 μM |
|---|---|
| Example 1 | 73 |
| Example 2 | 72 |
| Example 3 | 74 |
| Example 4 | 77 |
| Example 5 | 73 |
| Example 6 | 75 |
| Example 7 | 72 |
| Example 8 | 75 |
| Example 9 | 74 |
| Example 10 | 76 |
| Example 11 | 73 |
| Example 12 | 74 |
| Example 13 | 71 |
| Example 14 | 71 |
| Example 15 | 72 |
| Example 16 | 63 |
| Example 17 | 80 |
| Example 18 | 72 |
| Example 19 | 80 |
| Example 20 | 79 |
| Example 21 | 77 |
| Example 22 | 61 |
| Example 23 | 71 |
| Example 24 | 73 |
| Example 25 | 78 |
| Example 26 | 72 |
| Example 27 | 70 |
| Example 28 | 71 |
| Example 29 | 77 |
| Example 30 | 75 |
| Example 31 | 67 |
| Example 32 | 59 |
| Example 33 | 75 |
| Example 34 | 79 |
| Example 35 | 75 |
| Example 36 | 69 |

[Table 2-2]

Table 2 (continued)

| test compound | inhibitory rate (%) at 10 μM |
|---|---|
| Example 37 | 70 |
| Example 38 | 53 |
| Example 41 | 60 |
| Example 43 | 54 |
| Example 44 | 69 |
| Example 45 | 60 |
| Example 46 | 71 |
| Example 47 | 66 |
| Example 48 | 63 |
| Example 50 | 68 |
| Example 51 | 60 |
| Example 52 | 63 |
| Example 54 | 62 |
| Example 56 | 76 |
| Example 58 | 69 |
| Example 59 | 61 |
| Example 60 | 71 |
| Example 61 | 75 |
| Example 62 | 68 |
| Example 63 | 72 |
| Example 64 | 70 |
| Example 65 | 64 |
| Example 66 | 74 |
| Example 67 | 72 |
| Example 68 | 66 |
| Example 70 | 75 |
| Example 71 | 71 |
| Example 72 | 51 |
| Example 73 | 59 |
| Example 75 | 61 |
| Example 76 | 68 |
| Example 77 | 55 |
| Example 78 | 69 |
| Example 79 | 67 |
| Example 81 | 82 |
| Example 82 | 78 |
| Example 83 | 78 |

[Table 2-3]

Table 2 (continued)

| test compound | inhibitory rate (%) at 10 μM |
|---|---|
| Example 84 | 76 |
| Example 85 | 68 |
| Example 86 | 76 |
| Example 87 | 64 |
| Example 88 | 71 |
| Example 89 | 62 |
| Example 90 | 66 |
| Example 91 | 71 |
| Example 92 | 56 |
| Example A1 | 76 |
| Example A2 | 64 |
| Example A3 | 55 |
| Example A4 | 66 |
| Example A5 | 77 |
| Example A6 | 87 |
| Example A7 | 60 |
| Example A8 | 78 |
| Example A9 | 67 |
| Example A10 | 80 |
| Example A11 | 74 |
| Example A12 | 72 |
| Example A13 | 85 |
| Example A14 | 73 |
| Example A15 | 72 |
| Example A16 | 74 |
| Example A17 | 72 |
| Example A19 | 71 |
| Example A20 | 72 |
| Example A21 | 62 |
| Example A22 | 66 |
| Example A23 | 77 |
| Example A24 | 70 |
| Example A25 | 60 |
| Example A26 | 64 |
| Example A27 | 80 |
| Example A28 | 62 |
| Example A29 | 77 |

[Table 2-4]

Table 2 (continued)

| test compound | inhibitory rate (%) at 10 μM |
|---|---|
| Example A30 | 76 |
| Example A31 | 62 |
| Example A32 | 72 |
| Example A33 | 76 |
| Example A34 | 75 |
| Example A35 | 71 |
| Example A36 | 73 |
| Example A37 | 78 |
| Example A38 | 56 |
| Example A39 | 78 |
| Example A41 | 86 |
| Example A43 | 80 |
| Example A44 | 82 |
| Example A46 | 78 |
| Example A47 | 67 |
| Example A48 | 66 |
| Example A49 | 86 |
| Example A51 | 71 |
| Example A52 | 64 |
| Example A53 | 83 |
| Example A54 | 52 |
| Example A55 | 90 |
| Example A56 | 76 |
| Example A57 | 85 |
| Example A59 | 77 |
| Example A60 | 85 |
| Example A62 | 81 |
| Example A63 | 90 |
| Example A64 | 84 |
| Example A65 | 79 |
| Example A68 | 82 |
| Example A69 | 89 |
| Example A72 | 79 |
| Example A73 | 87 |
| Example A76 | 83 |
| Example A78 | 90 |
| Example A79 | 73 |

[Table 2-5]

Table 2 (continued)

| test compound | inhibitory rate (%) at 10 μM |
|---|---|
| Example A80 | 92 |
| Example A82 | 89 |
| Example A83 | 93 |
| Example A85 | 82 |
| Example A86 | 89 |
| Example A88 | 75 |
| Example A89 | 80 |
| Example A90 | 77 |
| Example A91 | 79 |
| Example A92 | 76 |
| Example A93 | 70 |
| Example A94 | 57 |
| Example A96 | 76 |
| Example A97 | 76 |
| Example A98 | 78 |
| Example A99 | 80 |
| Example A100 | 78 |
| Example A101 | 76 |
| Example A102 | 68 |
| Example A103 | 66 |
| Example A104 | 68 |
| Example A105 | 67 |
| Example A106 | 69 |
| Example A107 | 74 |
| Example A108 | 58 |
| Example A109 | 58 |
| Example A111 | 70 |
| Example A112 | 85 |
| Example A113 | 68 |
| Example A114 | 70 |
| Example A115 | 53 |
| Example A116 | 58 |
| Example A118 | 70 |
| Example A119 | 70 |
| Example A120 | 73 |
| Example A121 | 59 |
| Example A123 | 71 |

[Table 2-6]

Table 2 (continued)

| test compound | inhibitory rate (%) at 10 μM |
|---|---|
| Example A124 | 51 |
| Example A125 | 69 |
| Example A126 | 68 |
| Example A127 | 71 |
| Example A128 | 83 |
| Example A129 | 82 |
| Example A130 | 76 |
| Example A131 | 87 |
| Example A132 | 83 |
| Example A133 | 80 |
| Example A134 | 82 |
| Example A135 | 76 |
| Example A136 | 62 |
| Example A137 | 75 |
| Example A138 | 85 |
| Example A139 | 76 |
| Example A140 | 83 |
| Example A141 | 86 |
| Example A142 | 87 |
| Example A143 | 75 |
| Example A144 | 82 |
| Example A145 | 76 |
| Example A146 | 77 |
| Example A147 | 99 |
| Example A148 | 94 |
| Example A149 | 69 |
| Example A150 | 81 |
| Example A151 | 78 |
| Example A152 | 76 |
| Example A153 | 74 |
| Example A154 | 82 |
| Example A155 | 81 |
| Example A156 | 80 |
| Example A157 | 80 |
| Example A158 | 79 |
| Example A159 | 74 |
| Example A160 | 92 |

[Table 2-7]

Table 2 (continued)

| test compound | inhibitory rate (%) 10 μM |
|---|---|
| Example A161 | 84 |
| Example A162 | 79 |
| Example A163 | 87 |
| Example A164 | 85 |
| Example A165 | 85 |
| Example A166 | 75 |
| Example A167 | 86 |
| Example A168 | 90 |
| Example A169 | 86 |
| Example A170 | 89 |
| Example A171 | 86 |
| Example A172 | 82 |
| Example A173 | 74 |
| Example A174 | 98 |
| Example A175 | 68 |
| Example A176 | 96 |
| Example A177 | 90 |
| Example A178 | 86 |
| Example A179 | 84 |
| Example A180 | 83 |
| Example A181 | 88 |
| Example A182 | 95 |
| Example A183 | 88 |
| Example A184 | 74 |
| Example A185 | 71 |
| Example A186 | 85 |
| Example A187 | 90 |
| Example A188 | 77 |
| Example A190 | 86 |
| Example A191 | 82 |
| Example A192 | 72 |
| Example A193 | 80 |
| Example A194 | 88 |
| Example A195 | 84 |
| Example A196 | 87 |
| Example A198 | 87 |
| Example A199 | 88 |

[Table 2-8]

Table 2 (continued)

| test compound | inhibitory rate (%) at 10 μM |
|---|---|
| Example A200 | 89 |
| Example A202 | 86 |
| Example A204 | 86 |
| Example A206 | 70 |
| Example A208 | 83 |
| Example A209 | 90 |
| Example A211 | 70 |
| Example A213 | 70 |
| Example A214 | 75 |
| Example A215 | 72 |

[1745]

As mentioned above, it has been shown that the compound of the present invention has a superior glucagon binding inhibitory action.

[1746]

Experimental Example 2 suppressive action test for glucagon-induced blood glucose increase (rat)

Full feeding SD rats (male, 7- to 9-week-old) were fasted, 0.5% methylcellulose suspension containing a test compound (10 mg/kg body weight) (compound administration group, 5 rats per group) or 0.5% methylcellulose suspension (compound non-administration group, 12 rats per group) was orally administered, and 60 min later, glucagon (15 μg/kg body weight, Novo Nordisk Pharma Ltd.) was subcutaneously administered. At 20 min from the glucagon administration, blood samples were collected from the rat tail vein and the blood glucose was measured using a self-testing glucose kit ACCU-CHEK (Roche Diagnostics K.K.). In addition, as a non-treatment group (5 rats per group), the blood glucose of rat (compound non-treatment group) free of glucagon administration was measured in the same manner as above.

The difference between the blood glucose of compound non-

administration group or compound administration group and the blood glucose of non-treatment group was calculated. The percentage of "the difference between blood glucose of compound administration group and blood glucose of non-treatment group" was obtained as "blood glucose increase rate (% of control)" where "the difference between blood glucose of compound non-administration group and that of non-treatment group" is 100%. The results are shown in Table 3.

[1747]

Table 3

| test compound | compound administration dose (mg/kg) | blood glucose increasing rate (% of control) |
|---|---|---|
| Example A41 | 10 | 16.6 |
| Example A53 | 10 | 27.4 |
| Example A73 | 10 | 24.2 |
| Example A78 | 10 | 26.3 |
| Example A83 | 10 | 43.0 |

[1748]

As mentioned above, it has been shown that the compound of the present invention has a superior blood glucose increase-suppressive action.

[1749]

Formulation Example 1 (production of capsule)

| | | |
|---|---|---|
| 1) | compound of Example 1 | 30 mg |
| 2) | finely powdered cellulose | 10 mg |
| 3) | lactose | 19 mg |
| 4) | magnesium stearate | 1 mg |
| | Total | 60 mg |

1), 2), 3) and 4) are mixed and filled into a gelatin capsule.

[1750]

Formulation Example 2 (production of tablet)

| | | |
|---|---|---|
| 1) | compound of Example 1 | 30 g |
| 2) | lactose | 50 g |
| 3) | cornstarch | 15 g |
| 4) | calcium carboxymethylcellulose | 44 g |
| 5) | magnesium stearate | 1 g |
| | 1000 tablets total | 140 g |

Total amount of 1), 2) and 3) and 30 g of 4) are kneaded with water, dried in vacuo and sieved. To this sieved powder are added 14 g of 4) and 1 g of 5), and the mixture is tabletted by tableting machine. In this way, 1000 tablets containing 30 mg of Example 1 compound per tablet are obtained.

Industrial Applicability

[1751]

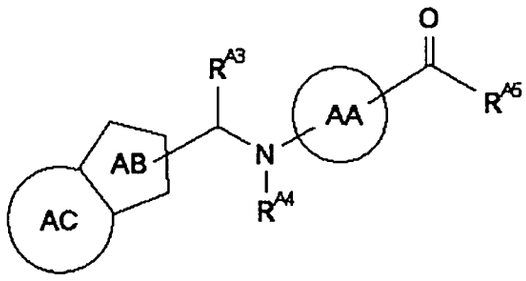
The compound of the present invention has a glucagon antagonistic action, and is useful for the prophylaxis or treatment of diabetes and the like.

[1752]

This application is based on patent application Nos. 2008-055250 and 2009-025511 filed in Japan, the contents of which are incorporated in full herein by this reference.

Claims

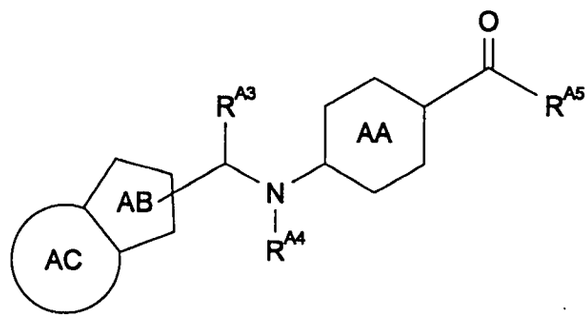
1. A compound represented by the following formula:




(IA)

wherein ring AA is an optionally substituted benzene ring, or an optionally substituted 5- or 6-membered aromatic heterocycle;
ring AB is an optionally substituted 5-membered aromatic heterocycle;
ring AC is an optionally substituted benzene ring, or an optionally substituted 5- or 6-membered aromatic heterocycle;
$R^{A3}$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{3-10}$ cycloalkyl group, an optionally substituted $C_{6-14}$ aryl group or an optionally substituted heterocyclic group;
$R^{A4}$ is a hydrogen atom or a $C_{1-6}$ alkyl group;
$R^{A5}$ is $-(CH_2)_3-COOR^{A11}$ or $-NR^{A6}-CR^{A7}R^{A8}-CR^{A9}R^{A10}-COOR^{A11}$;
$R^{A6}$, $R^{A7}$, $R^{A8}$, $R^{A9}$ and $R^{A11}$ are each independently a hydrogen atom or a $C_{1-6}$ alkyl group; and
$R^{A10}$ is a hydrogen atom, a $C_{1-6}$ alkyl group or a hydroxy group, or a salt thereof.

2. The compound of claim 1, wherein the formula (IA) is the following formula




(IA')

, and

ring AA is a benzene ring or 6-membered aromatic heterocycle.

3. The compound of claim 2, wherein $R^{A3}$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{3-10}$ cycloalkyl group, or an optionally substituted 5- or 6-membered heterocyclic group;
$R^{A4}$ is a hydrogen atom;
$R^{A5}$ is $-(CH_2)_3-COOR^{A11}$ or $-NR^{A6}-(CH_2)_2-COOR^{A11}$;
$R^{A6}$ is a hydrogen atom or methyl; and
$R^{A11}$ is a hydrogen atom, methyl or ethyl.

4. 3-{[(4-{[Cyclohexyl(3-methyl-1-benzofuran-2-yl)methyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid or a salt thereof.

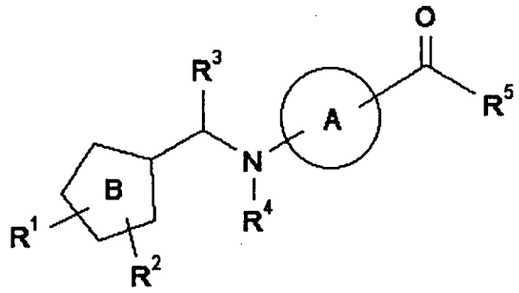
5. 3-{[(6-{[Cyclohexyl(5-fluoro-3-methyl-1-benzofuran-2-yl)methyl]amino}pyridin-3-yl)carbonyl](methyl)amino}propanoic acid or a salt thereof.

6. 3-{[(4-{[2-Ethyl-1-(5-fluoro-3-methyl-1-benzofuran-2-yl)butyl]amino}phenyl)carbonyl](methyl)amino}propanoic acid or a salt thereof.

7. 3-[{[4-({1-[5-(Cyclopropylmethoxy)-3-methyl-1-benzofuran-2-yl]-2-methylpropyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid or a salt thereof.

8. 3-[{[4-({Cyclohexyl[3-methyl-5-(tetrahydro-2H-pyran-4-yloxy)-1-benzofuran-2-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid or a salt thereof.

9. A compound represented by the following formula:



(I)

wherein ring A is an optionally substituted benzene ring, or an optionally substituted 5- or 6-membered aromatic heterocycle;

ring B is pyrazole;

$R^1$ and $R^2$ are each independently an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted hydroxy group or acyl;

$R^3$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{3-10}$ cycloalkyl group, an optionally substituted $C_{6-14}$ aryl group or an optionally substituted heterocyclic group;

$R^4$ is a hydrogen atom or a $C_{1-6}$ alkyl group;

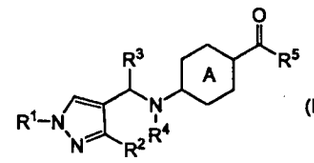
$R^5$ is $-(CH_2)_3-COOR^{11}$ or $-NR^6-CR^7R^8-CR^9R^{10}-COOR^{11}$;

$R^6$, $R^7$, $R^8$, $R^9$ and $R^{11}$ are each independently a hydrogen atom or a $C_{1-6}$ alkyl group; and

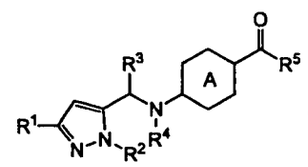
$R^{10}$ is a hydrogen atom, a $C_{1-6}$ alkyl group or a hydroxy group,

excluding N-[4-[[(1-phenyl-5-propyl-1H-pyrazol-4-yl)methyl]amino]benzoyl]-β-alanine, or a salt thereof.

10. The compound of claim 9, wherein the formula (I) is the following formula

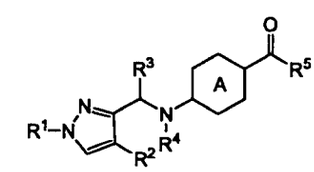


(I')



(I'')

or



(I''')

,

and ring A is a benzene ring or 6-membered aromatic heterocycle.

11. The compound of claim 9, wherein $R^1$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{6-14}$

aryl group, or an optionally substituted 5- or 6-membered aromatic heterocyclic group;

$R^2$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{1-6}$ alkoxy group, or an optionally substituted $C_{3-10}$ cycloalkyl group;

$R^3$ is an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{3-10}$ cycloalkyl group, or an optionally substituted 5- or 6-membered heterocyclic group;

$R^4$ is a hydrogen atom;

$R^5$ is $-(CH_2)_3-COOR^{11}$ or $-NR^6-CH_2-CR^9R^{10}-COOR^{11}$;

$R^6$ is a hydrogen atom or methyl;

$R^9$ is a hydrogen atom, methyl or ethyl;

$R^{10}$ is a hydrogen atom, methyl or ethyl; and

$R^{11}$ is a hydrogen atom, methyl or ethyl.

12. 3-[({4-[(Cyclohexyl{3-methyl-1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}methyl)amino]phenyl}carbonyl)amino]propanoic acid or a salt thereof.

13. 3-[{[4-({Cyclohexyl[1-(3-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid or a salt thereof.

14. 3-[{[4-({Cyclohexyl[1-(3-methoxyphenyl)-4-methyl-1H-pyrazol-3-yl]methyl}amino)phenyl]carbonyl}(methyl)amino]propanoic acid or a salt thereof.

15. A prodrug of the compound of claim 1 or 9.

16. A medicament comprising the compound of claim 1 or 9, or a prodrug thereof.

17. The medicament of claim 16 which is a glucagon antagonist.

18. The medicament of claim 16 which is a sugar production-suppressive agent.

19. The medicament of claim 16 which is an agent for the prophylactic or treatment of diabetes.

20. A method of suppressing sugar production in a mammal, comprising administering the compound of claim 1 or a prodrug thereof or the compound of claim 9 or a prodrug thereof to the mammal.

21. A method for the prophylaxis or treatment of diabetes in a mammal, comprising administering the compound of claim 1 or a prodrug thereof or the compound of claim 9 or a prodrug thereof to the mammal.

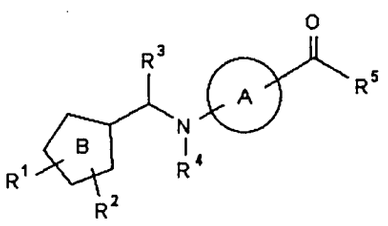
22. Use of the compound of claim 1 or a prodrug thereof or the compound of claim 9 or a prodrug thereof for the production of a medicament for suppressing sugar production.

23. Use of the compound of claim 1 or a prodrug thereof or the compound of claim 9 or a prodrug thereof for the production of an agent for the prophylaxis or treatment of diabetes.

## Abstract

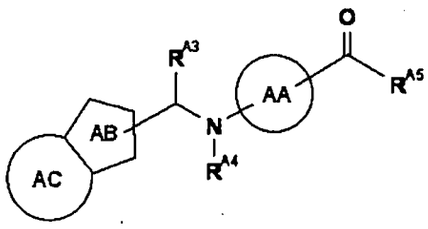
Provision of a prophylactic or therapeutic agent for diabetes, which has superior efficacy.

A compound represented by the formula:




(I)

or




(IA)

wherein each symbol is as described in the specification, or a salt thereof.

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# COMPUESTO HETEROCÍCLICO

## Campo técnico

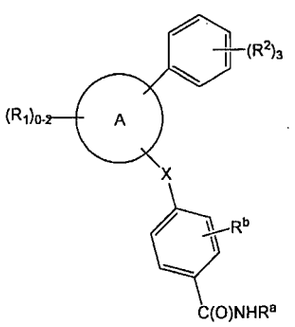
La presente invención se refiere a un compuesto heterocíclico con acción antagonista del glucagón, el cual es útil para la profilaxis o el tratamiento de diabetes y similares.

## Antecedentes de la invención

El glucagón es una hormona peptídica de cadena lineal que contiene 29 aminoácidos, la cual es secretada por las células α pancreáticas y promueve la glucogenólisis y la gluconeogénesis en el hígado. Los pacientes con diabetes, en general, presentan aumento de la secreción y reactividad al glucagón, lo cual es una de las causas de la hiperglucemia. En consecuencia, los antagonistas de receptor de glucagón pueden suprimir el exceso de producción de azúcar por parte del hígado, al cortar las acciones del glucagón y son útiles como fármacos terapéuticos contra la diabetes.

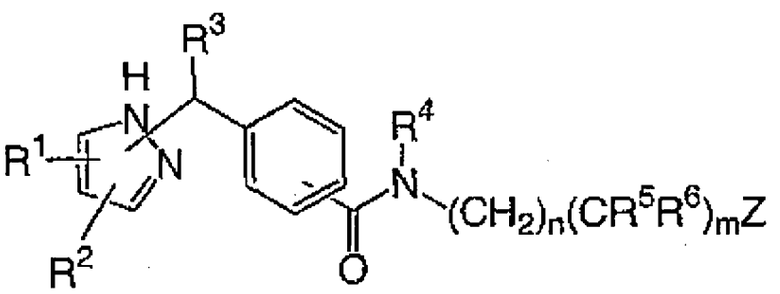
Como antagonistas de glucagón, se conocen los siguientes compuestos.

1) un compuesto representado por la siguiente fórmula:



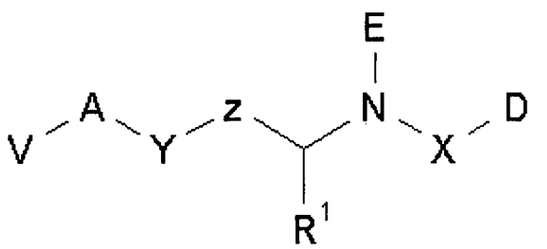
en donde el anillo A es arilo de 6 a 10 miembros, grupo heterocíclico aromático de 6 a 10 miembros, arilo de 6 miembros condensado con un carbociclo de 5 ó 6 miembros; $R_1$ es, cuando está presente, (a) halógeno, OH, $CO_2R^4$, $SO_pR^5$, CN, $NO_2$, $C(O)NR^6R^7$ o $NR^6R^7$, (b) alquilo $C_{1-6}$, C(O)alquilo $C_{1-6}$ o C(O)alquilo $C_{1-6}$ (sustituible con (a)), (c) arilo de 6 a 10 miembros, ariloxi o ariltio o grupo heterocíclico aromático de 5 a 10 miembros, heterociclil-oxi aromático o heterociclil-tio aromático (cada uno sustituible con (a) o (b); estos grupos también son sustituibles con pirazol, imidazol, tetrazol, pirrol, triazol, tiazol, furano, tiofeno, tiadiazol u oxazol (cada uno sustituible con (a) o (b))); $R^2$ es H o sustituyente (a) o (b); X es -O-, -S-, $-(C(R^3)_2)_{1-2}-$, $-OC(R^3)_2-$ o $-C(R^3)_2O-$; $R^3$ es H o alquilo $C_{1-10}$, alquenilo C2-4, arilo o grupo heterocíclico aromático (sustituible con (a) o (b); uno de $R^3$ es distinto de H o alquilo $C_{1-10}$); $R^4$ es H o alquilo $C_{1-6}$; $R^5$ es alquilo $C_{1-10}$, arilo o aril-alquilo $C_{1-10}$; $R^6$ y $R^7$ son cada uno H o alquilo $C_{1-3}$; p es 0 - 2; $R^a$ es $CH_2CH_2CO_2R^4$, $CH_2CH(OH)CO_2R^4$ o 5-tetrazolilo; y $R^b$ es H o sustituyente (a) o (b)] (documento de patente 1: WO 2006/102067).

2) Un compuesto representado por la siguiente fórmula:



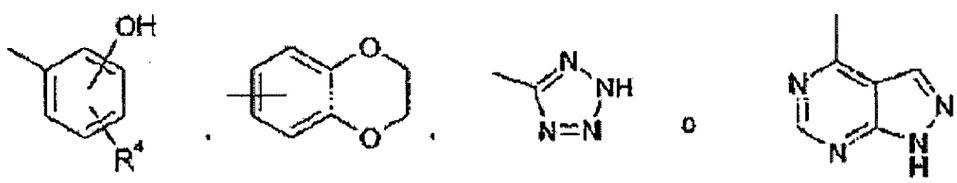
en donde $R^1$ es (a) alquilo $C_{1-10}$, alquenilo $C_{2-10}$ o alquinilo $C_{2-10}$ (cada uno sustituible) o (b) arilo, grupo heterocíclico aromático o grupo heterocíclico no aromático (cada uno sustituible); $R^2$ es H o $R^1$; $R^3$ y $R^4$ son cada uno H o alquilo $C_{1-10}$; $R^5$ es H o F; $R^6$ es H, OH, F o alquilo $C_{1-3}$ o $R^5$ y $R^6$ forman oxo; $R^8$ es H o alquilo $C_{1-10}$ (sustituible con fenilo, OH, Oalquilo $C_{1-6}$, $CO_2H$, $CO_2$alquilo $C_{1-6}$, halo); m es 0 - 2; n es 1 - 6; cuando uno de m y n es distinto de 0, Z es $COR^8$, 5-tetrazolilo o 5-(2-oxo-1,3,4-oxadiazolilo) y cuando m y n son ambos 0, Z es 5-tetrazolilo o 5-(2-oxo-1,3,4-oxadiazolilo)] (documento de patente 2: WO 2004/069158).

3) Un compuesto representado por la siguiente fórmula:




(I)

en donde V es $-C(O)OR^2$, $-C(O)NR^2R^3$, $-C(O)NR^2OR^3$, $-S(O)_2OR^2$,




;

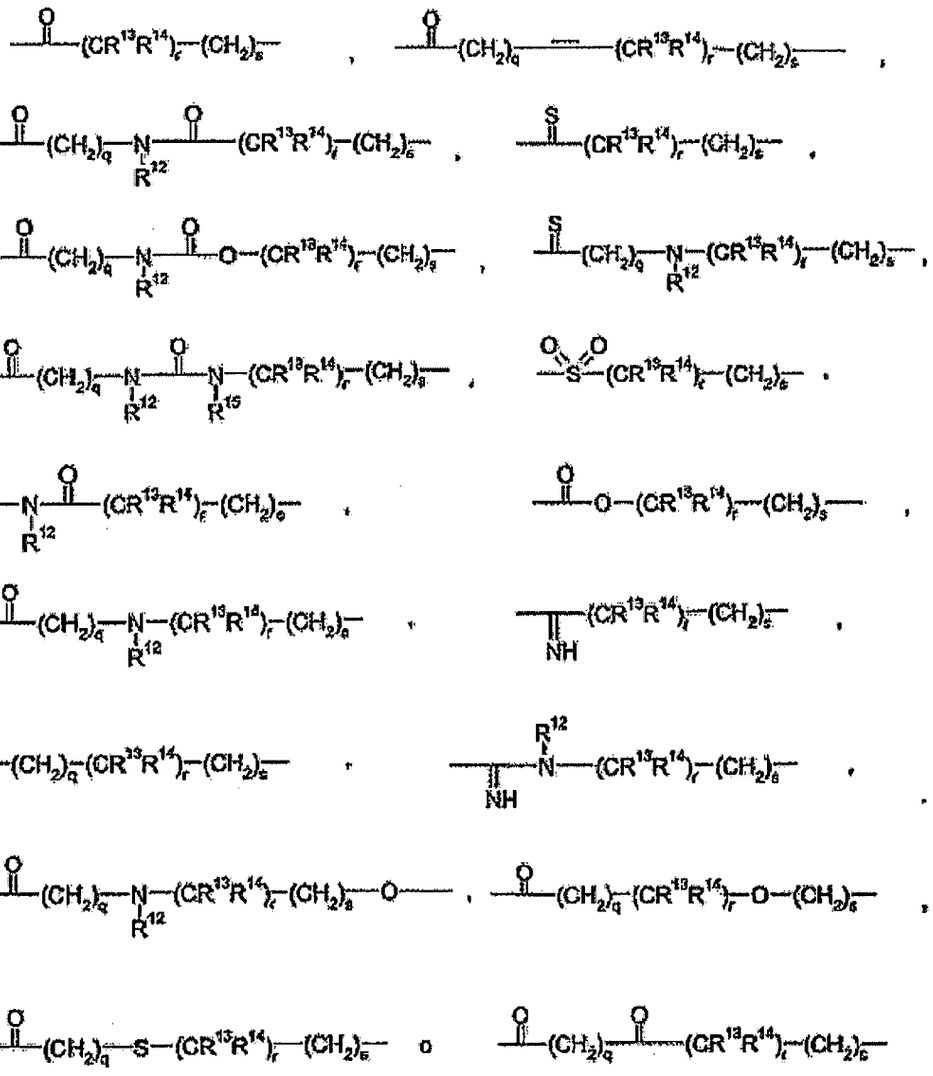
$R^2$ y $R^3$ son cada uno, de modo independiente, H o alquilo $C_{1-6}$; $R^4$ es H, halógeno y similares; A es




;

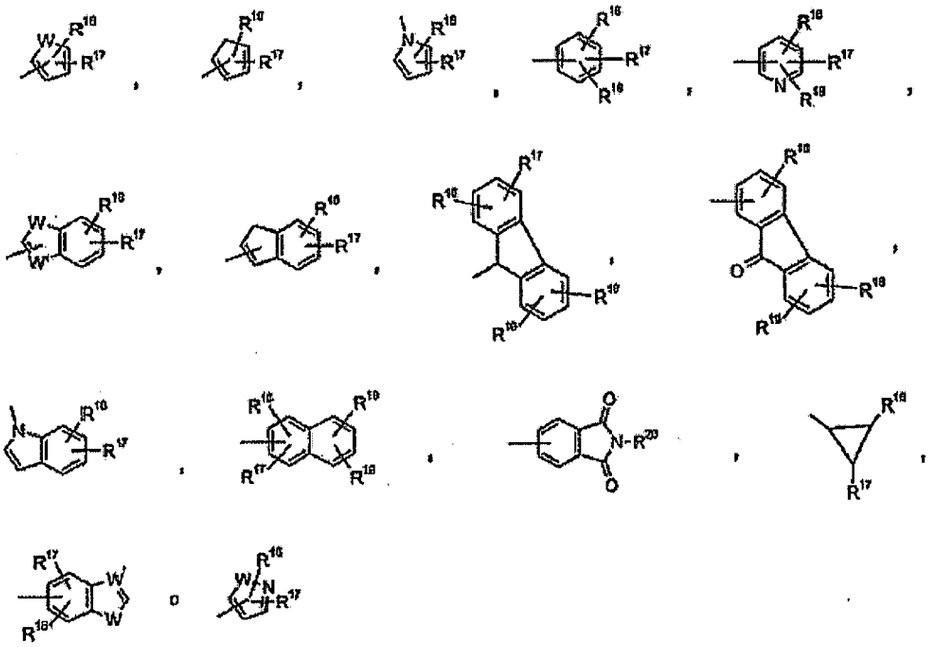
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b es 0 ó 1; n es 0 - 3; $R^7$ es H, alquilo $C_{1-6}$ y similares; $R^8$ y $R^9$ son cada uno, de modo independiente, H o alquilo $C_{1-6}$; Y es $-C(O)-$, $-S(O)_2-$, $-O-$ o un enlace; Z es fenilo, 5 - un heterociclo aromático de 6 miembros (cada uno sustituible con halo, etc.); $R^1$ es H o alquilo $C_{1-6}$; X es



;

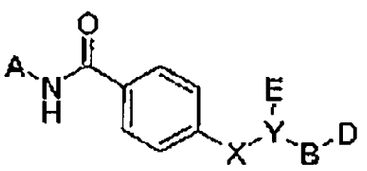
r es 0 ó 1; q y s son cada uno 0 - 3; $R^{12}$, $R^{13}$, $R^{14}$ y $R^{15}$ son cada uno, de modo independiente, H o alquilo $C_{1-6}$; D es



;

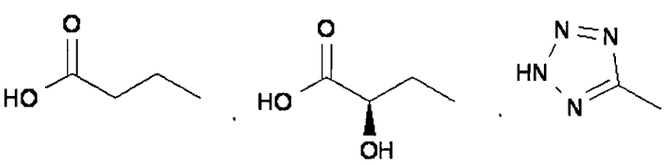
W es -O-, -S-, $-S(O)_2-$ o $-NR^{20}-$; W' is $=CR^{20'}-$ o -N=; $R^{16}$, $R^{17}$, $R^{18}$ y $R^{19}$ son cada uno, de modo independiente, H, $-C(O)NR^{21}R^{22}$, $-C(O)R^{21}$ y similares; $R^{20}$ y $R^{20'}$ son cada uno H, alquilo $C_{1-6}$, cicloalquilo $C_{3-8}$ o cicloalquil $C_{3-8}$-alquilo $C_{1-6}$; $R^{21}$ y $R^{22}$ son cada uno H, $-CF_3$, alquilo $C_{1-6}$, arilo, grupo heterocíclico aromático y similares; y E es un anillo monocíclico o bicíclico opcionalmente sustituido de 3 a 9 miembros (documento de patente 3: WO 00/69810).

4) Un compuesto representado por la siguiente fórmula:



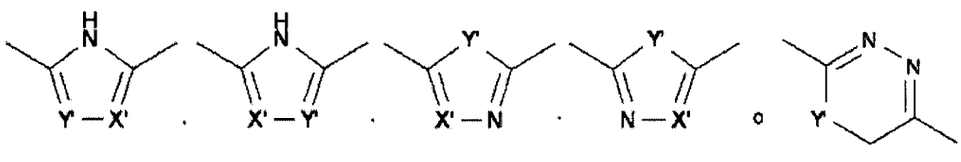
(I)

en donde A es



;

X es un enlace, $-CR^1R^2-$ o $-NR^1-$; Y es $>CR^3-$ o $>N-$; $R^1$, $R^2$ y $R^3$ son cada uno, de modo independiente, H o alquilo $C_{1-6}$ o $R^1$ y $R^2$ forman opcionalmente un enlace doble; E es alquilo $C_{1-10}$ o cicloalquilo $C_{3-10}$, cicloalquil $C_{3-10}$-alquilo $C_{1-6}$, arilo, grupo heterocíclico aromático o aril-alquilo $C_{1-6}$ (estos son cada uno sustituible con halógeno, alquilo $C_{1-6}$, etc.) y similares; B es

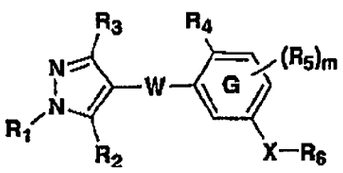


;

X' es $-N=$ o $-CR^8=$; Y' es -S-, -O- o $NR^8-$; $R^8$ es H o alquilo $C_{1-6}$ o arilo (son cada uno sustituibles con halógeno, alquilo $C_{1-6}$, etc.); $R^9$ es H o alquilo $C_{1-6}$; D es arilo o grupo heterocíclico aromático (cada uno sustituible con halógeno, alquilo $C_{1-10}$, alcoxi $C_{1-6}$, cicloalquilo $C_{3-8}$, arilo (estos anillos son sustituibles con halógeno, alquilo $C_{1-10}$, etc.) y similares) (documento de patente 4: WO 2004/002480).

Además, se conocen los siguientes compuestos.

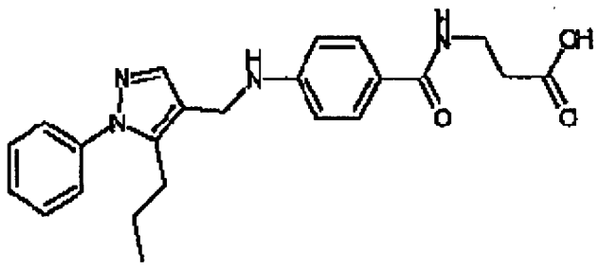
5) Un compuesto representado por la siguiente fórmula



(I),

en donde G es fenilo o piridilo; W es $-NH(C=O)(CHR_8)_r-$, $-CH(R_8)NH-$, $-NHCH(R_8)-$, $-CH_2-O-$ o $-(C=O)O-$; $R_8$ es H o alquilo; r es 0, 1 ó 2; $R_1$ es H, alquilo opcionalmente sustituido, arilo opcionalmente sustituido, grupo heterocíclico aromático opcionalmente sustituido, cicloalquilo opcionalmente

sustituido, grupo heterocíclico no aromático opcionalmente sustituido y similares; $R_2$ es H, alquilo opcionalmente sustituido, alcoxi opcionalmente sustituido, amino y similares; $R_3$ es H, $-CF_3$, $-OCF_3$, halógeno, alquilo C1-4 opcionalmente sustituido, $-OR_{11}$ y similares; $R_4$ es H, alquilo C1-4 opcionalmente sustituido, halógeno, $-CF_3$, $-OCF_3$, $-OR_{13}$ y similares; $R_5$ es $-CF_3$, $-OCF_3$, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, grupo heterocíclico no aromático opcionalmente sustituido, arilo opcionalmente sustituido, grupo heterocíclico aromático opcionalmente sustituido, $-OR_{13}$, $-C(=O)R_{13}$, $-C(=O)NR_{13}R_{14}$ y similares; X es $-(C=O)NH-$, $-NH(C=O)-$, $-NH(C=O)O-$, $-SO_2NH-$, $-CO_2-$ o un enlace; $R_6$ es H, alquilo C1-4 opcionalmente sustituido, alcoxi opcionalmente sustituido, fenoxi opcionalmente sustituido, cicloalquilo opcionalmente sustituido, grupo heterocíclico no aromático opcionalmente sustituido, arilo opcionalmente sustituido, grupo heterocíclico aromático opcionalmente sustituido y similares; $R_6$ y $R_5$ pueden estar unidos entre sí para formar un anillo de 5 ó 6 miembros; $R_{11}$, $R_{13}$ y $R_{14}$ son cada uno, de modo independiente, H, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, grupo heterocíclico no aromático opcionalmente sustituido, arilo opcionalmente sustituido o heterociclo aromático opcionalmente sustituido; m es 0, 1, 2 ó 3, que es de utilidad como un agente terapéutico para enfermedades inflamatorias, específicamente el siguiente compuesto



(documento de patente 5: WO 2004/098528).

documento de patente 1: WO 2006/102067

documento de patente 2: WO 2004/069158

documento de patente 3: WO 00/69810

documento de patente 4: WO 2004/002480

documento de patente 5: WO 2004/098528

**Descripción de la invención**

Problemas por resolver por medio de la invención

Se deseaba el desarrollo de un compuesto que tuviera una eficacia superior y que fuese de utilidad para la prevención o el tratamiento de diabetes y similares.

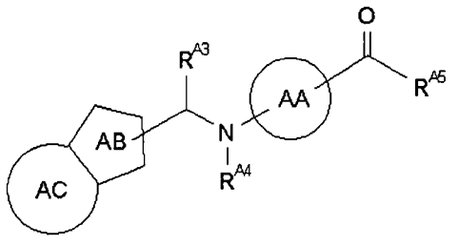
Medios para resolver los problemas

Los presentes inventores hallaron que un compuesto representado por la siguiente fórmula (I) o una de sus sales (a veces abreviado como "compuesto (I)" en la presente memoria descriptiva) y un compuesto representado por la fórmula (IA) o una de sus sales (a veces abreviado como "compuesto (IA)" en la presente memoria descriptiva) tienen una superior acción antagonista de glucagón y una superior eficacia como un agente para la terapia y el tratamiento de diabetes y similares. En base a este hallazgo, los presentes

inventores realizaron estudios intensivos y completaron la presente invención.

Conforme a ello, la presente invención se refiere a

(1) un compuesto representado por la siguiente fórmula:




(IA)

en donde el anillo AA es un anillo benceno opcionalmente sustituido o un heterociclo aromático de 5 ó 6 miembros opcionalmente sustituido;

el anillo AB es un heterociclo aromático de 5 miembros opcionalmente sustituido;

el anillo AC es un anillo benceno opcionalmente sustituido o un heterociclo aromático de 5 ó 6 miembros opcionalmente sustituido;

$R^{A3}$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, es un grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido, es un grupo arilo $C_{6-14}$ opcionalmente sustituido o un grupo heterocíclico opcionalmente sustituido;

$R^{A4}$ es un átomo de hidrógeno o un grupo alquilo $C_{1-6}$;

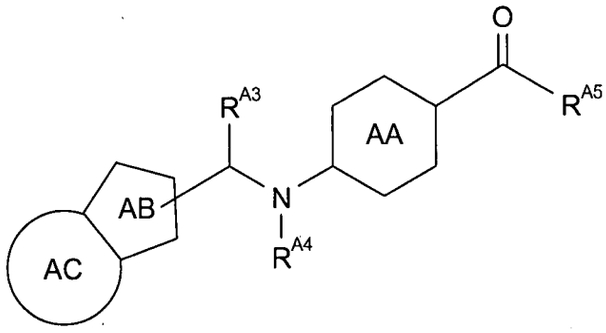
$R^{A5}$ es $-(CH_2)_3-COOR^{A11}$ o $-NR^{A6}-CR^{A7}R^{A8}-CR^{A9}R^{A10}-COOR^{A11}$;

$R^{A6}$, $R^{A7}$, $R^{A8}$, $R^{A9}$ y $R^{A11}$ son cada uno, de modo independiente, un átomo de hidrógeno o un grupo alquilo $C_{1-6}$; y

$R^{A10}$ es un átomo de hidrógeno, un grupo alquilo $C_{1-6}$ o un grupo hidroxi,

o una de sus sales;

(2) el compuesto del punto (1) antes mencionado, en donde la fórmula (IA) es la siguiente fórmula




(IA'),

, y

el anillo AA es un anillo benceno o un heterociclo aromático de 6 miembros;

(3) el compuesto del punto (2) antes mencionado, en donde $R^{A3}$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, es un grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido o un grupo heterocíclico de 5 ó 6 miembros opcionalmente sustituido;

$R^{A4}$ es un átomo de hidrógeno;

$R^{A5}$ es $-(CH_2)_3-COOR^{A11}$ o $-NR^{A6}-(CH_2)_2-COOR^{A11}$;

$R^{A6}$ es un átomo de hidrógeno o metilo; y

$R^{A11}$ es un átomo de hidrógeno, metilo o etilo;

(4) ácido 3-{[(4-{[ciclohexil(3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico o una de sus sales;

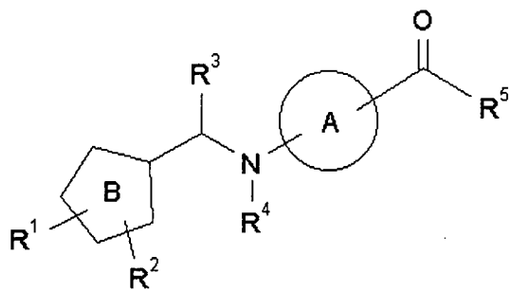
(5) ácido 3-{[(6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil](metil)amino}propanoico o una de sus sales;

(6) ácido 3-{[(4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil](metil)amino}propanoico o una de sus sales;

(7) ácido 3-[{[4-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico o una de sus sales;

(8) ácido 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico o una de sus sales;

(9) un compuesto representado por la siguiente fórmula:




(I)

en donde el anillo A es un anillo benceno opcionalmente sustituido o un heterociclo aromático de 5 ó 6 miembros opcionalmente sustituido;

el anillo B es pirazol;

$R^1$ y $R^2$ son cada uno, de modo independiente, un grupo hidrocarburo opcionalmente sustituido, un grupo heterocíclico opcionalmente sustituido, un grupo hidroxi opcionalmente sustituido o acilo;

$R^3$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, es un grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido, es un grupo arilo $C_{6-14}$ opcionalmente sustituido o un grupo heterocíclico opcionalmente sustituido;

$R^4$ es un átomo de hidrógeno o un grupo alquilo $C_{1-6}$;

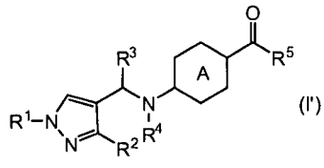
$R^5$ es $-(CH_2)_3-COOR^{11}$ o $-NR^6-CR^7R^8-CR^9R^{10}-COOR^{11}$;

$R^6$, $R^7$, $R^8$, $R^9$ y $R^{11}$ son cada uno, de modo independiente, un átomo de hidrógeno o un grupo alquilo $C_{1-6}$; y

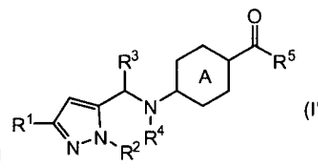
$R^{10}$ es un átomo de hidrógeno, un grupo alquilo $C_{1-6}$ o un grupo hidroxi,

excluyendo N-[4-[[(1-fenil-5-propil-1H-pirazol-4-il)metil]amino]benzoil]-β-alanina o una de sus sales;

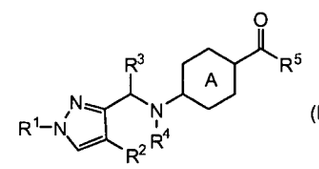
(10) el compuesto del punto (9) antes mencionado, en donde la fórmula (I) es la siguiente fórmula


(I')

o


(I")

o


(I'")

y el anillo A es un anillo benceno o un heterociclo aromático de 6 miembros;

(11) el compuesto del punto (9) antes mencionado, en donde $R^1$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, es un grupo arilo $C_{6-14}$ opcionalmente sustituido o un grupo heterocíclico aromático de 5 ó 6 miembros opcionalmente sustituido;

$R^2$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, un grupo alcoxi $C_{1-6}$ opcionalmente sustituido o es un grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido;

$R^3$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, es un grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido o un grupo heterocíclico de 5 ó 6 miembros opcionalmente sustituido;

$R^4$ es un átomo de hidrógeno;

$R^5$ es $-(CH_2)_3-COOR^{11}$ o $-NR^6-CH_2-CR^9R^{10}-COOR^{11}$;

$R^6$ es un átomo de hidrógeno o metilo;

$R^9$ es un átomo de hidrógeno, metilo o etilo;

$R^{10}$ es un átomo de hidrógeno, metilo o etilo; y

$R^{11}$ es un átomo de hidrógeno, metilo o etilo;

(12) ácido 3-[({4-[(ciclohexil{3-metil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico o una de sus sales;

(13) ácido 3-[{[4-({ciclohexil[1-(3-metoxifenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico o una de sus sales;

(14) ácido 3-[{[4-({ciclohexil[1-(3-metoxifenil)-4-metil-1H-pirazol-3-il]metil}amino)fenil]carbonil}(metil)amino]propanoico o una de sus sales;

(15) un profármaco del compuesto del punto (1) u (9) antes mencionado;

(16) un medicamento que comprende el compuesto del punto (1) u (9) antes mencionado o uno de sus profármacos;

(17) el medicamento del punto (16) antes mencionado que es un antagonista de glucagón;

(18) el medicamento del punto (16) antes mencionado que es un agente supresor de la producción de azúcar;

(19) el medicamento del punto (16) antes mencionado que es un agente para la terapia o el tratamiento de diabetes;

(20) un método de supresión de la producción de azúcar en un mamífero, que comprende la administración del compuesto del punto (1) antes mencionado o uno de sus profármacos o el compuesto del punto (9) antes mencionado o uno de sus profármacos al mamífero;

(21) un método para la profilaxis o el tratamiento de diabetes en un mamífero, que comprende la administración del compuesto del punto (1) antes mencionado o uno de sus profármacos o el compuesto del punto (9) antes mencionado o uno de sus profármacos al mamífero;
(22) uso del compuesto del punto (1) antes mencionado o uno de sus profármacos o el compuesto del punto (9) antes mencionado o uno de sus profármacos para la fabricación de un medicamento para la supresión de la producción de azúcar;
(23) uso del compuesto del punto (1) antes mencionado o uno de sus profármacos o el compuesto del punto (9) antes mencionado o uno de sus profármacos para la producción de un agente para la profilaxis o el tratamiento de diabetes;
y similares.

Efecto de la invención

Como el compuesto de la presente invención tiene una acción antagonista de glucagón y una superior eficacia (supresión del aumento de glucosa en sangre, acción hipoglucémica y similares), es de utilidad para la prevención o el tratamiento de diabetes y similares.

**Descripción detallada de la invención**

En la presente memoria descriptiva, el "átomo de halógeno" significa un átomo de flúor, un átomo de cloro, un átomo de bromo o un átomo de yodo.

En la presente memoria descriptiva, los ejemplos del "grupo alquilo $C_{1-10}$" incluyen metilo, etilo, propilo,

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isopropilo, butilo, isobutilo, sec-butilo, ter-butilo, pentilo, isopentilo, neopentilo, 1-etilpropilo, hexilo, isohexilo, 1,1-dimetilbutilo, 2,2-dimetilbutilo, 3,3-dimetilbutilo, 2-etilbutilo, heptilo, octilo, nonilo, decilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo alquilo $C_{1-6}$" incluyen metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, ter-butilo, pentilo, isopentilo, neopentilo, 1-etilpropilo, hexilo, isohexilo, 1,1-dimetilbutilo, 2,2-dimetilbutilo, 3,3-dimetilbutilo, 2-etilbutilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo alquilo $C_{1-6}$ ramificado" incluyen isopropilo, isobutilo, sec-butilo, ter-butilo, isopentilo, neopentilo, 1-etilpropilo, isohexilo, 1,1-dimetilbutilo, 2,2-dimetilbutilo, 3,3-dimetilbutilo, 2-etilbutilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo alquenilo $C_{2-10}$" incluyen etenilo, 1-propenilo, 2-propenilo, 2-metil-1-propenilo, 1-butenilo, 2-butenilo, 3-butenilo, 3-metil-2-butenilo, 1-pentenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 4-metil-3-pentenilo, 1-hexenilo, 3-hexenilo, 5-hexenilo, 1-heptenilo, 1-octenilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo alquenilo $C_{2-6}$" incluyen etenilo, 1-propenilo, 2-propenilo, 2-metil-1-propenilo, 1-butenilo, 2-butenilo, 3-butenilo, 3-metil-2-butenilo, 1-pentenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 4-metil-3-pentenilo, 1-hexenilo, 3-hexenilo, 5-hexenilo y similares.

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En la presente memoria descriptiva, los ejemplos del "grupo alquinilo $C_{2-10}$" incluyen etinilo, 1-propinilo, 2-propinilo, 1-butinilo, 2-butinilo, 3-butinilo, 1-pentinilo, 2-pentinilo, 3-pentinilo, 4-pentinilo, 1-hexinilo, 2-hexinilo, 3-hexinilo, 4-hexinilo, 5-hexinilo, 1-heptinilo, 1-octinilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo alquinilo $C_{2-6}$" incluyen etinilo, 1-propinilo, 2-propinilo, 1-butinilo, 2-butinilo, 3-butinilo, 1-pentinilo, 2-pentinilo, 3-pentinilo, 4-pentinilo, 1-hexinilo, 2-hexinilo, 3-hexinilo, 4-hexinilo, 5-hexinilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo alcoxi $C_{1-6}$" incluyen metoxi, etoxi, propoxi, isopropoxi, butoxi, isobutoxi, sec-butoxi, ter-butoxi y similares.

En la presente memoria descriptiva, los ejemplos del "grupo alquenil $C_{2-6}$-oxi" incluyen eteniloxi y similares.

En la presente memoria descriptiva, los ejemplos del "grupo cicloalquilo $C_{3-10}$" incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, biciclo[2,2,1]heptilo, biciclo[2,2,2]octilo, biciclo[3,2,1]octilo, biciclo[3,2,2]nonilo, biciclo[3,3,1]nonilo, biciclo[4,2,1]nonilo, biciclo[4,3,1]decilo, adamantilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo cicloalquilo $C_{3-6}$" incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y similares.

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El grupo cicloalquilo $C_{3-6}$ y el grupo cicloalquilo $C_{3-10}$ pueden formar un grupo de anillo fusionado con un anillo benceno y los ejemplos de tal grupo de anillo fusionado incluyen indanilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo cicloalquenilo $C_{3-10}$" incluyen ciclopropenilo (por ejemplo, 2-ciclopropen-1-ilo), ciclobutenilo (por ejemplo, 2-ciclobuten-1-ilo), ciclopentenilo (por ejemplo, 2-ciclopenten-1-ilo, 3-ciclopenten-1-ilo), ciclohexenilo (por ejemplo, 2-ciclohexen-1-ilo, 3-ciclohexen-1-ilo), cicloheptenilo (por ejemplo, 2-ciclohepten-1-ilo), ciclooctenilo (por ejemplo, 2-cicloocten-1-ilo) y similares.

En la presente memoria descriptiva, los ejemplos del "grupo cicloalquenilo $C_{3-6}$" incluyen ciclopropenilo (por ejemplo, 2-ciclopropen-1-ilo), ciclobutenilo (por ejemplo, 2-ciclobuten-1-ilo), ciclopentenilo (por ejemplo, 2-ciclopenten-1-ilo, 3-ciclopenten-1-ilo), ciclohexenilo (por ejemplo, 2-ciclohexen-1-ilo, 3-ciclohexen-1-ilo) y similares.

El grupo cicloalquenilo $C_{3-6}$ y el grupo cicloalquenilo $C_{3-10}$ pueden formar un grupo de anillo fusionado con un anillo benceno y los ejemplos de tal grupo de anillo fusionado incluyen dihidronaftilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo cicloalcadienilo $C_{4-10}$" incluyen 2,4-ciclopentadien-1-ilo, 2,4-ciclohexadien-1-ilo, 2,5-ciclohexadien-1-ilo y similares.

El grupo cicloalcadienilo $C_{4-10}$ puede formar un grupo de anillo fusionado con un anillo benceno y los ejemplos de tal grupo de anillo fusionado incluyen fluorenilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo arilo $C_{6-14}$" incluyen fenilo, naftilo, antrilo, fenantrilo, acenaftilo, bifenililo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo arilo $C_{6-10}$" incluyen fenilo, naftilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo aril $C_{6-14}$-oxi" incluyen feniloxi y naftiloxi.

En la presente memoria descriptiva, los ejemplos del "grupo aralquilo $C_{7-13}$" incluyen bencilo, fenetilo, naftilmetilo, bifenililmetilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo aralquil $C_{7-13}$-oxi" incluyen benciloxi y similares.

En la presente memoria descriptiva, los ejemplos del "grupo arilalquenilo $C_{8-13}$" incluyen estirilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo heterocíclico" incluyen los siguientes grupos heterocíclicos aromáticos y no aromáticos.

En la presente memoria descriptiva, los ejemplos del "grupo heterocíclico aromático" incluyen un grupo heterocíclico aromático de 4 a 12 miembros, por ejemplo, un grupo heterocíclico aromático monocíclico de 4 a 7 miembros (con preferencia, de 5 ó 6 miembros) que contiene, como un átomo constitutivo del anillo además de átomos de carbono, 1 a 4 heteroátomos seleccionados de un átomo de oxígeno, un átomo de azufre (opcionalmente oxidado) y un átomo de

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818

nitrógeno y un grupo heterocíclico aromático fusionado de 8 a 12 miembros. Los ejemplos del grupo heterocíclico aromático fusionado incluyen un grupo derivado de un anillo fusionado en donde 1 ó 2 anillos seleccionados de un heterociclo aromático de 5 ó 6 miembros que contiene 1 ó 2 átomos de nitrógeno (por ejemplo, pirrol, imidazol, pirazol, pirazina, piridina, pirimidina), un heterociclo aromático de 5 miembros que contiene un átomo de azufre (por ejemplo, tiofeno) y un anillo benceno y un anillo correspondiente a un grupo heterocíclico aromático monocíclico de 4 a 7 miembros son condensados y similares.

Los ejemplos preferidos del grupo heterocíclico aromático incluyen
grupos heterocíclicos aromáticos monocíclicos tales como furilo (por ejemplo, 2-furilo, 3-furilo), tienilo (por ejemplo, 2-tienilo, 3-tienilo), piridilo (por ejemplo, 2-piridilo, 3-piridilo, 4-piridilo), pirimidinilo (por ejemplo, 2-pirimidinilo, 4-pirimidinilo, 5-pirimidinilo), piridazinilo (por ejemplo, 3-piridazinilo, 4-piridazinilo), pirazinilo (por ejemplo, 2-pirazinilo), pirrolilo (por ejemplo, 1-pirrolilo, 2-pirrolilo, 3-pirrolilo), imidazolilo (por ejemplo, 1-imidazolilo, 2-imidazolilo, 4-imidazolilo, 5-imidazolilo), pirazolilo (por ejemplo, 1-pirazolilo, 3-pirazolilo, 4-pirazolilo), tiazolilo (por ejemplo, 2-tiazolilo, 4-tiazolilo, 5-tiazolilo), isotiazolilo (por ejemplo, 3-isotiazolilo, 4-isotiazolilo, 5-isotiazolilo), oxazolilo (por ejemplo, 2-oxazolilo, 4-oxazolilo, 5-oxazolilo), isoxazolilo (por ejemplo, 3-isoxazolilo, 4-

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isoxazolilo, 5-isoxazolilo), oxadiazolilo (por ejemplo, 1,2,4-oxadiazol-5-ilo, 1,3,4-oxadiazol-2-ilo), tiadiazolilo (por ejemplo, 1,3,4-tiadiazol-2-ilo), triazolilo (por ejemplo, 1,2,4-triazol-1-ilo, 1,2,4-triazol-3-ilo, 1,2,3-triazol-1-ilo, 1,2,3-triazol-2-ilo, 1,2,3-triazol-4-ilo), tetrazolilo (por ejemplo, tetrazol-1-ilo, tetrazol-5-ilo), triazinilo (por ejemplo, 1,2,4-triazin-1-ilo, 1,2,4-triazin-3-ilo) y similares;

grupos heterocíclicos aromáticos fusionados tales como quinolilo (por ejemplo, 2-quinolilo, 3-quinolilo, 4-quinolilo, 6-quinolilo), isoquinolilo (por ejemplo, 3-isoquinolilo), quinazolilo (por ejemplo, 2-quinazolilo, 4-quinazolilo), quinoxalilo (por ejemplo, 2-quinoxalilo, 6-quinoxalilo), benzofuranilo (por ejemplo, 2-benzofuranilo, 3-benzofuranilo), benzotienilo (por ejemplo, 2-benzotienilo, 3-benzotienilo), benzoxazolilo (por ejemplo, 2-benzoxazolilo), benzisoxazolilo (por ejemplo, 7-benzisoxazolilo), benzotiazolilo (por ejemplo, 2-benzotiazolilo), bencimidazolilo (por ejemplo, bencimidazol-1-ilo, bencimidazol-2-ilo, bencimidazol-5-ilo), benzotriazolilo (por ejemplo, 1H-1,2,3-benzotriazol-5-ilo), indolilo (por ejemplo, indol-1-ilo, indol-2-ilo, indol-3-ilo, indol-5-ilo), indazolilo (por ejemplo, 1H-indazol-3-ilo), pirrolopirazinilo (por ejemplo, 1H-pirrolo[2,3-b]pirazin-2-ilo, 1H-pirrolo[2,3-b]pirazin-6-ilo), imidazopiridinilo (por ejemplo, 1H-imidazo[4,5-b]piridin-2-ilo, 1H-imidazo[4,5-c]piridin-2-ilo, 2H-imidazo[1,2-a]piridin-3-ilo), tienopiridinilo (por ejemplo, tieno[2,3-b]piridin-3-ilo), imidazopirazinilo (por

ejemplo, 1H-imidazo[4,5-b]pirazin-2-ilo), pirazolopiridinilo (por ejemplo, 1H-pirazolo[4,3-c]piridin-3-ilo), pirazolotienilo (por ejemplo, 2H-pirazolo[3,4-b]tiofen-2-ilo), pirazolotriazinilo (por ejemplo, pirazolo[5,1-c][1,2,4]triazin-3-ilo) y similares;
y similares.

En la presente memoria descriptiva, los ejemplos del "grupo heterocíclico no aromático" incluyen un grupo heterocíclico no aromático de 4 a 12 miembros, por ejemplo, un grupo heterocíclico no aromático monocíclico de 4 a 7 miembros (con preferencia 5 ó 6 miembros) que contiene, como un átomo constitutivo del anillo además de átomos de carbono, 1 a 4 heteroátomos seleccionados de un átomo de oxígeno, un átomo de azufre (el átomo de azufre está opcionalmente oxidado) y un átomo de nitrógeno y un grupo heterocíclico no aromático fusionado de 8 a 12 miembros. Los ejemplos del grupo heterocíclico no aromático fusionado incluyen un grupo derivado de un anillo fusionado en donde 1 ó 2 anillos seleccionados de un heterociclo aromático de 5 ó 6 miembros que contiene 1 ó 2 átomos de nitrógeno (por ejemplo, pirrol, imidazol, pirazol, pirazina, piridina, pirimidina), un heterociclo aromático de 5 miembros que contiene un átomo de azufre (por ejemplo, tiofeno) y un anillo benceno y un anillo correspondiente al grupo heterocíclico no aromático monocíclico de 4 a 7 miembros son condensados (opcionalmente, también parcialmente saturados) y similares.

Los ejemplos preferidos del grupo heterocíclico no aromático incluyen

grupos heterocíclicos no aromáticos monocíclicos tales como oxetanilo (por ejemplo, 3-oxetanilo), pirrolidinilo (por ejemplo, 1-pirrolidinilo, 2-pirrolidinilo), piperidinilo (por ejemplo, piperidino, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo), morfolinilo (por ejemplo, morfolino), tiomorfolinilo (por ejemplo, tiomorfolino), piperazinilo (por ejemplo, 1-piperazinilo, 2-piperazinilo, 3-piperazinilo), hexametileniminilo (por ejemplo, hexametilenimin-1-ilo), oxazolidinilo (por ejemplo, oxazolidin-2-ilo), tiazolidinilo (por ejemplo, tiazolidin-2-ilo), dihidrotiopiranilo (por ejemplo, dihidrotiopiran-3-ilo, dihidrotiopiran-4-ilo), imidazolidinilo (por ejemplo, imidazolidin-2-ilo, imidazolidin-3-ilo), oxazolinilo (por ejemplo, oxazolin-2-ilo), tiazolinilo (por ejemplo, tiazolin-2-ilo), imidazolinilo (por ejemplo, imidazolin-2-ilo, imidazolin-3-ilo), dioxolilo (por ejemplo, 1,3-dioxol-4-ilo), dioxolanilo (por ejemplo, 1,3-dioxolan-4-ilo), dihidrooxadiazolilo (por ejemplo, 4,5-dihidro-1,2,4-oxadiazol-3-ilo), piranilo (por ejemplo, 4-piranilo), tetrahidropiranilo (por ejemplo, 2-tetrahidropiranilo, 3-tetrahidropiranilo, 4-tetrahidropiranilo), tiopiranilo (por ejemplo, 4-tiopiranilo), tetrahidrotiopiranilo (por ejemplo, 2-tetrahidrotiopiranilo, 3-tetrahidrotiopiranilo, 4-tetrahidrotiopiranilo), 1-oxidotetrahidrotiopiranilo (por ejemplo, 1-oxidotetrahidrotiopiran-4-ilo), 1,1-dioxidotetrahidrotiopiranilo (por ejemplo, 1,1-dioxidotetrahidrotiopiran-4-ilo), tetrahidrofurilo (por ejemplo, tetrahidrofurano-3-ilo, tetrahidrofurano-2-ilo),

pirazolidinilo (por ejemplo, pirazolidin-1-ilo, pirazolidin-3-ilo), pirazolinilo (por ejemplo, pirazolin-1-ilo), tetrahidropirimidinilo (por ejemplo, tetrahidropirimidin-1-ilo), dihidrotriazolilo (por ejemplo, 2,3-dihidro-1H-1,2,3-triazol-1-ilo), tetrahidrotriazolilo (por ejemplo, 2,3,4,5-tetrahidro-1H-1,2,3-triazol-1-ilo) y similares;
grupos heterocíclicos no aromáticos fusionados tales como dihidroindolilo (por ejemplo, 2,3-dihidro-1H-indol-1-ilo), dihidroisoindolilo (por ejemplo, 1,3-dihidro-2H-isoindol-2-ilo), dihidrobenzofuranilo (por ejemplo, 2,3-dihidro-1-benzofuran-5-ilo), dihidrobenzodioxinilo (por ejemplo, 2,3-dihidro-1,4-benzodioxinilo), dihidrobenzodioxepinilo (por ejemplo, 3,4-dihidro-2H-1,5-benzodioxepinilo), tetrahidrobenzofuranilo (por ejemplo, 4,5,6,7-tetrahidro-1-benzofuran-3-ilo), cromenilo (por ejemplo, 4H-cromen-2-ilo, 2H-cromen-3-ilo), dihidrocromenilo (por ejemplo, 3,4-dihidro-2H-cromen-2-ilo), dihidroquinolinilo (por ejemplo, 1,2-dihidroquinolin-4-ilo), tetrahidroquinolinilo (por ejemplo, 1,2,3,4-tetrahidroquinolin-4-ilo), dihidroisoquinolinilo (por ejemplo, 1,2-dihidroisoquinolin-4-ilo), tetrahidroisoquinolinilo (por ejemplo, 1,2,3,4-tetrahidroisoquinolin-4-ilo), dihidroftalazinilo (por ejemplo, 1,4-dihidroftalazin-4-ilo) y similares;
y similares.

En la presente memoria descriptiva, los ejemplos del "grupo heterocíclico de 5 ó 6 miembros" incluyen anillo de 5 ó 6 miembros de entre los grupos heterocíclicos aromáticos

monocíclicos y los grupos heterocíclicos no aromáticos monocíclicos antes mencionados.

En la presente memoria descriptiva, los ejemplos específicos del "heterociclo aromático de 5 ó 6 miembros" incluyen anillos correspondientes al grupo de anillo de 5 ó 6 miembros de entre los grupos heterocíclicos aromáticos antes mencionados, por ejemplo, furano, tiofeno, piridina, pirimidina, piridazina, pirazina, pirrol, imidazol, pirazol, tiazol, isotiazol, oxazol, isoxazol, oxadiazol, tiadiazol, triazol, tetrazol, triazina, y similares.

En la presente memoria descriptiva, los ejemplos específicos del "heterociclo aromático de 5 miembros" incluyen anillos correspondientes a los grupos de anillo de 5 miembros de entre los grupos heterocíclicos aromáticos antes mencionados, por ejemplo, furano, tiofeno, pirrol, imidazol, pirazol, tiazol, isotiazol, oxazol, isoxazol, oxadiazol, tiadiazol, triazol, tetrazol, y similares.

En la presente memoria descriptiva, los ejemplos del "grupo heterociclil-oxi aromático de 4 a 12 miembros" incluyen grupos en donde un grupo oxi está unido con el grupo heterocíclico aromático de 4 a 12 miembros antes mencionado, por ejemplo, piridiloxi y similares.

En la presente memoria descriptiva, los ejemplos del "grupo heterociclil-oxi no aromático de 4 a 12 miembros" incluyen grupos en donde un grupo oxi está unido con el grupo heterocíclico no aromático de 4 a 12 miembros antes mencionado, por ejemplo, tetrahidropiraniloxi,

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tetrahidrotiopiraniloxi, 1,1-dioxidotetrahidrotiopiraniloxi y similares.

En la presente memoria descriptiva, los ejemplos del "grupo heterociclil-carbonilo aromático de 4 a 12 miembros" incluyen grupos en donde un grupo carbonilo está unido con el grupo heterocíclico aromático de 4 a 12 miembros antes mencionado, por ejemplo, furilcarbonilo, tienilcarbonilo, pirazolilcarbonilo, pirazinilcarbonilo, isooxazolilcarbonilo, piridilcarbonilo, tiazolilcarbonilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo heterociclil-carbonilo no aromático de 4 a 12 miembros" incluyen grupos en donde un grupo carbonilo está unido con el grupo heterocíclico no aromático de 4 a 12 miembros, por ejemplo, tetrahidrofurilcarbonilo, pirrolidinilcarbonilo, morfolinilcarbonilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo alquil $C_{1-6}$-carbonilo" incluyen acetilo, propanoilo, butanoilo, isobutanoilo, ter-butanoilo, pentanoilo, isopentanoilo, hexanoilo, y similares.

En la presente memoria descriptiva, los ejemplos del "grupo alquil $C_{1-6}$-carboniloxi" incluyen acetiloxi, propanoiloxi, butanoiloxi, isobutanoiloxi, ter-butanoiloxi, pentanoiloxi, isopentanoiloxi, hexanoiloxi y similares.

En la presente memoria descriptiva, los ejemplos del "grupo alcoxi $C_{1-6}$-carbonil" incluyen metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, ter-butoxicarbonilo y similares.

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En la presente memoria descriptiva, los ejemplos del "grupo cicloalquil $C_{3-10}$-carbonilo" incluyen ciclopropilcarbonilo, ciclopentilcarbonilo, ciclohexilcarbonilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo aril $C_{6-14}$-carbonilo" incluyen benzoilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo alquil $C_{1-6}$-tio" incluyen metiltio, etiltio, isopropiltio y similares.

En la presente memoria descriptiva, los ejemplos del "grupo aril $C_{6-14}$-tio" incluyen feniltio, naftiltio y similares.

En la presente memoria descriptiva, los ejemplos del "grupo aralquil $C_{7-13}$-tio" incluyen benciltio y similares.

En la presente memoria descriptiva, los ejemplos del "grupo alquil $C_{1-6}$-sulfonilo" incluyen metilsulfonilo, etilsulfonilo, isopropilsulfonilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo aril $C_{6-14}$-sulfonilo" incluyen bencensulfonilo y similares.

En la presente memoria descriptiva, los ejemplos del "grupo alquilen $C_{1-3}$-dioxi" incluyen metilendioxi, etilendioxi y similares.

En la presente memoria descriptiva, los ejemplos del "grupo hidrocarburo opcionalmente sustituido" incluyen grupo alquilo $C_{1-10}$ opcionalmente sustituido, grupo alquenilo $C_{2-10}$ opcionalmente sustituido, grupo alquinilo $C_{2-10}$ opcionalmente sustituido, grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido,

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grupo cicloalquenilo $C_{3-10}$ opcionalmente sustituido, grupo cicloalcadienilo $C_{4-10}$ opcionalmente sustituido y grupo arilo $C_{6-14}$ opcionalmente sustituido, grupo aralquilo $C_{7-13}$ opcionalmente sustituido, grupo arilalquenilo $C_{8-13}$ opcionalmente sustituido y similares.

En la presente memoria descriptiva, los ejemplos del "grupo hidroxi opcionalmente sustituido" incluyen un grupo hidroxi opcionalmente sustituido con sustituyentes seleccionados de

(1) grupo alquilo $C_{1-10}$ opcionalmente sustituido (con preferencia, grupo alquilo $C_{1-6}$ opcionalmente sustituido),

(2) grupo alquenilo $C_{2-10}$ opcionalmente sustituido,

(3) grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido,

(4) grupo cicloalquenilo $C_{3-10}$ opcionalmente sustituido,

(5) grupo arilo $C_{6-14}$ opcionalmente sustituido,

(6) grupo aralquilo $C_{7-13}$ opcionalmente sustituido,

(7) grupo arilalquenilo $C_{8-13}$ opcionalmente sustituido,

(8) grupo alquil $C_{1-6}$-carbonilo opcionalmente sustituido,

(9) grupo heterocíclico opcionalmente sustituido

y similares.

En la presente memoria descriptiva, el grupo alquilo $C_{1-6}$, grupo alquilo $C_{1-10}$, grupo alquenilo $C_{2-10}$, grupo alquinilo $C_{2-10}$ y grupo alquil $C_{1-6}$-carbonilo del "grupo alquilo $C_{1-6}$ opcionalmente sustituido", "grupo alquilo $C_{1-10}$ opcionalmente sustituido", "grupo alquenilo $C_{2-10}$ opcionalmente sustituido", "grupo alquinilo $C_{2-10}$ opcionalmente sustituido" y "grupo alquil $C_{1-6}$-carbonilo opcionalmente sustituido" tienen

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opcionalmente 1 a 5 (con preferencia 1 a 3) sustituyentes en cada una de las posiciones sustituibles.

Los ejemplos de tal sustituyente incluyen el siguiente grupo de sustituyentes A:

(grupo A de sustituyentes)

(1) grupo cicloalquilo $C_{3-10}$;

(2) grupo arilo $C_{6-14}$ opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno,

(b) grupo hidroxi,

(c) grupo alcoxi $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno y

(d) átomo de halógeno;

(3) grupo heterocíclico aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno,

(b) grupo hidroxi,

(c) grupo alcoxi $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno y

(d) átomo de halógeno;

(4) grupo heterocíclico no aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno,

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(b) grupo hidroxi,

(c) grupo alcoxi $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno,

(d) átomo de halógeno y

(e) grupo oxo;

(5) grupo amino opcionalmente mono- o disustituido con sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(i) átomo de halógeno y

(ii) grupo alcoxi $C_{1-6}$,

(b) grupo alquil $C_{1-6}$-carbonilo opcionalmente sustituido con 1 a 3 átomos de halógeno,

(c) grupo alcoxi $C_{1-6}$-carbonilo opcionalmente sustituido con 1 a 3 átomos de halógeno,

(d) grupo alquil $C_{1-6}$-sulfonilo opcionalmente sustituido con 1 a 3 átomos de halógeno,

(e) grupo carbamoilo opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno y

(f) grupo heterocíclico aromático de 4 a 12 miembros;

(6) grupo alquil $C_{1-6}$-carbonilo opcionalmente sustituido con 1 a 3 átomos de halógeno;

(7) grupo alcoxi $C_{1-6}$-carbonilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) grupo alcoxi $C_{1-6}$ y

(c) grupo arilo $C_{6-14}$;

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(8) grupo alquil $C_{1-6}$-sulfonilo opcionalmente sustituido con 1 a 3 átomos de halógeno;

(9) grupo carbamoilo opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno;

(10) grupo tiocarbamoilo opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno;

(11) grupo sulfamoilo opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno;

(12) grupo carboxi;

(13) grupo hidroxi;

(14) grupo alcoxi $C_{1-6}$ opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) grupo carboxi,

(c) grupo alcoxi $C_{1-6}$,

(d) grupo cicloalquilo $C_{3-6}$,

(e) grupo alcoxi $C_{1-6}$-carbonilo opcionalmente sustituido con 1 a 3 grupos arilo $C_{6-14}$,

(f) grupo amino opcionalmente mono- o disustituido con sustituyentes seleccionados de grupo alquilo $C_{1-6}$ y grupo alcoxi $C_{1-6}$-carbonilo,

(g) grupo heterocíclico aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(i) átomo de halógeno y

(ii) grupo alquilo $C_{1-6}$,

(h) grupo heterocíclico no aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 grupos alquilo $C_{1-6}$,

(i) grupo alquil $C_{1-6}$-sulfonilo,

(j) grupo alquil $C_{1-6}$-tio y

(k) grupo hidroxi;

(15) grupo alquenil $C_{2-6}$-oxi opcionalmente sustituido con 1 a 3 átomos de halógeno;

(16) grupo aralquil $C_{7-13}$-oxi;

(17) grupo aril $C_{6-14}$-oxi;

(18) grupo alquil $C_{1-6}$-carboniloxi;

(19) grupo heterociclil-oxi aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(i) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno y

(ii) grupo ciano;

(20) grupo heterociclil-oxi no aromático de 4 a 12 miembros;

(21) grupo aril $C_{6-14}$-carbonilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno y

(b) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno;

(22) grupo heterociclil-carbonilo aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno;

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(23) grupo heterociclil-carbonilo no aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno;

(24) grupo mercapto;

(25) grupo alquil $C_{1-6}$-tio opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno y

(b) grupo alcoxi $C_{1-6}$-carbonilo;

(26) grupo aralquil $C_{7-13}$-tio;

(27) grupo aril $C_{6-14}$-tio;

(28) grupo ciano;

(29) grupo nitro;

(30) átomo de halógeno;

(31) grupo alquilen $C_{1-3}$-dioxi.

Cuando se usan dos o más sustituyentes, los respectivos sustituyentes pueden ser iguales o diferentes.

En la presente memoria descriptiva, el anillo benceno, grupo arilo $C_{6-14}$, grupo cicloalquenilo $C_{3-10}$, grupo cicloalcadienilo $C_{4-10}$, grupo aralquilo $C_{7-13}$ y grupo arilalquenilo $C_{8-13}$ del "anillo benceno opcionalmente sustituido", "grupo arilo $C_{6-14}$ opcionalmente sustituido", "grupo cicloalquenilo $C_{3-10}$ opcionalmente sustituido", "grupo cicloalcadienilo $C_{4-10}$ opcionalmente sustituido", "grupo aralquilo $C_{7-13}$ opcionalmente sustituido" y "grupo arilalquenilo $C_{8-13}$ opcionalmente sustituido" tienen cada uno opcionalmente 1 a 5 (con preferencia 1 a 3) sustituyentes en posiciones sustituibles.

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Los ejemplos de tal sustituyente incluyen el siguiente grupo B de sustituyentes:

(grupo B de sustituyentes)

(1) grupo cicloalquilo $C_{3-10}$;

(2) grupo arilo $C_{6-14}$ opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno,

(b) grupo hidroxi,

(c) grupo alcoxi $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno y

(d) átomo de halógeno;

(3) grupo heterocíclico aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno,

(b) grupo hidroxi,

(c) grupo alcoxi $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno y

(d) átomo de halógeno;

(4) grupo heterocíclico no aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno,

(b) grupo hidroxi,

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(c) grupo alcoxi $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno,

(d) átomo de halógeno y

(e) grupo oxo;

(5) grupo amino opcionalmente mono- o disustituido con sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(i) átomo de halógeno y

(ii) grupo alcoxi $C_{1-6}$,

(b) grupo alquil $C_{1-6}$-carbonilo opcionalmente sustituido con 1 a 3 átomos de halógeno,

(c) grupo alcoxi $C_{1-6}$-carbonilo opcionalmente sustituido con 1 a 3 átomos de halógeno,

(d) grupo alquil $C_{1-6}$-sulfonilo opcionalmente sustituido con 1 a 3 átomos de halógeno,

(e) grupo carbamoilo opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno,

(f) grupo heterocíclico aromático de 4 a 12 miembros,

(g) grupo aril $C_{6-14}$-carbonilo (por ejemplo, benzoilo),

(h) grupo aril $C_{6-14}$-sulfonilo (por ejemplo, bencensulfonilo) y

(i) grupo aralquilo $C_{7-13}$ (por ejemplo, bencilo);

(6) grupo alquil $C_{1-6}$-carbonilo opcionalmente sustituido con 1 a 3 átomos de halógeno;

(7) grupo alcoxi $C_{1-6}$-carbonilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

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(a) átomo de halógeno,

(b) grupo alcoxi $C_{1-6}$ y

(c) grupo arilo $C_{6-14}$;

(8) grupo alquil $C_{1-6}$-sulfonilo opcionalmente sustituido con 1 a 3 átomos de halógeno;

(9) grupo carbamoilo opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno;

(10) grupo tiocarbamoilo opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno;

(11) grupo sulfamoilo opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno;

(12) grupo carboxi;

(13) grupo hidroxi;

(14) grupo alcoxi $C_{1-6}$ opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) grupo carboxi,

(c) grupo alcoxi $C_{1-6}$,

(d) grupo cicloalquilo $C_{3-6}$,

(e) grupo alcoxi $C_{1-6}$-carbonilo opcionalmente sustituido con 1 a 3 grupo arilo $C_{6-14}$s,

(f) grupo amino opcionalmente mono- o disustituido con sustituyentes seleccionados de grupo alquilo $C_{1-6}$ y grupo alcoxi $C_{1-6}$-carbonilo,

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(g) grupo heterocíclico aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(i) átomo de halógeno y

(ii) grupo alquilo $C_{1-6}$,

(h) grupo heterocíclico no aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 grupos alquilo $C_{1-6}$,

(i) grupo alquil $C_{1-6}$-sulfonilo,

(j) grupo alquil $C_{1-6}$-tio y

(k) grupo hidroxi;

(15) grupo alquenil $C_{2-6}$-oxi opcionalmente sustituido con 1 a 3 átomos de halógeno;

(16) grupo aralquil $C_{7-13}$-oxi;

(17) grupo aril $C_{6-14}$-oxi;

(18) grupo alquil $C_{1-6}$-carboniloxi;

(19) grupo heterociclil-oxi aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(i) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno y

(ii) grupo ciano;

(20) grupo heterociclil-oxi no aromático de 4 a 12 miembros;

(21) grupo aril $C_{6-14}$-carbonilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno y

(b) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno;

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(22) grupo heterociclil-carbonilo aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno;

(23) grupo heterociclil-carbonilo no aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno;

(24) grupo mercapto;

(25) grupo alquil $C_{1-6}$-tio opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno y

(b) grupo alcoxi $C_{1-6}$-carbonilo;

(26) grupo aralquil $C_{7-13}$-tio;

(27) grupo aril $C_{6-14}$-tio;

(28) grupo ciano;

(29) grupo nitro;

(30) átomo de halógeno;

(31) grupo alquilen $C_{1-3}$-dioxi;

(32) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) grupo carboxi,

(c) grupo hidroxi,

(d) grupo alcoxi $C_{1-6}$-carbonilo,

(e) grupo alcoxi $C_{1-6}$ opcionalmente sustituido con 1 a 3 grupos alcoxi $C_{1-6}$ y

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(f) grupo amino opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$;

(33) grupo alquenilo $C_{2-6}$ opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) grupo carboxi,

(c) grupo hidroxi,

(d) grupo alcoxi $C_{1-6}$-carbonilo,

(e) grupo alcoxi $C_{1-6}$ y

(f) grupo amino opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$(s); y

(34) grupo aralquilo $C_{7-13}$ opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno,

(b) grupo hidroxi,

(c) grupo alcoxi $C_{1-6}$ y

(d) átomo de halógeno.

Cuando se usan dos o más sustituyentes, los respectivos sustituyentes pueden ser iguales o diferentes.

En la presente memoria descriptiva, el grupo cicloalquilo $C_{3-10}$ del "grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido" tiene opcionalmente 1 a 5 (con preferencia 1 a 3) sustituyentes en posiciones sustituibles. Los ejemplos de tal sustituyente incluyen el grupo B de sustituyentes antes mencionado y el grupo oxo. Cuando se usan dos o más sustituyentes, los respectivos sustituyentes pueden ser iguales o diferentes.

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En la presente memoria descriptiva, cuando el "grupo heterocíclico" y "grupo heterocíclico de 5 ó 6 miembros" del "grupo heterocíclico opcionalmente sustituido" y "grupo heterocíclico de 5 ó 6 miembros opcionalmente sustituido" son grupos heterocíclicos aromáticos, los grupos heterocíclicos aromáticos tienen opcionalmente 1 a 5 (con preferencia 1 a 3) sustituyentes en posiciones sustituibles.

Los ejemplos de tal sustituyente incluyen el grupo B de sustituyentes antes mencionado. Cuando se usan dos o más sustituyentes, los respectivos sustituyentes pueden ser iguales o diferentes.

En la presente memoria descriptiva, cuando el "grupo heterocíclico" y "grupo heterocíclico de 5 ó 6 miembros" del "grupo heterocíclico opcionalmente sustituido" y "grupo heterocíclico opcionalmente sustituido de 5 ó 6 miembros" son grupos heterocíclicos no aromáticos, los grupos heterocíclicos no aromáticos tienen opcionalmente 1 a 5 (con preferencia 1 a 3) sustituyentes en posiciones sustituibles.

Los ejemplos de tal sustituyente incluyen el grupo B de sustituyentes antes mencionado y grupo oxo. Cuando se usan dos o más sustituyentes, los respectivos sustituyentes pueden ser iguales o diferentes.

En la presente memoria descriptiva, el heterociclo aromático de 5 ó 6 miembros y el heterociclo aromático de 5 miembros del "heterociclo aromático de 5 ó 6 miembros opcionalmente sustituido" y "heterociclo aromático de 5 miembros opcionalmente sustituido" tienen cada uno opcionalmente 1 a 5 (con preferencia 1 a 3) sustituyentes en

posiciones sustituibles. Los ejemplos de tal sustituyente incluyen el grupo B de sustituyentes antes mencionado. Cuando se usan dos o más sustituyentes, los respectivos sustituyentes pueden ser iguales o diferentes.

En la presente memoria descriptiva, los ejemplos del "acilo" incluyen grupos representado por la fórmulas: $-CO-R^A$, $-CO-OR^A$, $-S(O)_3-R^A$, $-S(O)_2-R^A$, $-S(O)-R^A$, $-CO-NR^{A'}R^{B'}$, $-CS-NR^{A'}R^{B'}$, $-S(O)_2-NR^{A'}R^{B'}$ y similares.

En la fórmula, $R^A$ es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo heterocíclico opcionalmente sustituido. $R^{A'}$ y $R^{B'}$ son cada uno, de modo independiente, un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo heterocíclico opcionalmente sustituido o $R^{A'}$ y $R^{B'}$ forman, junto con el átomo de nitrógeno adyacente, un heterociclo no aromático opcionalmente sustituido que contiene nitrógeno.

Los ejemplos del te "heterociclo no aromático que contiene nitrógeno" del "heterociclo no aromático opcionalmente sustituido que contiene nitrógeno" formado por $R^{A'}$ y $R^{B'}$, junto con el átomo de nitrógeno adyacente, incluyen heterociclo no aromático de 5 a 7 miembros que contiene nitrógeno, como un átomo constitutivo del anillo además de átomo de carbono, al menos un átomo de nitrógeno y también opcionalmente que contiene 1 ó 2 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre (el átomo de azufre puede estar oxidado) y átomo de nitrógeno. Los ejemplos preferidos de tal heterociclo no aromático que contiene

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nitrógeno incluyen pirrolidina, imidazolidina, pirazolidina, piperidina, piperazina, morfolina, tiomorfolina y similares.

El heterociclo no aromático que contiene nitrógeno tiene opcionalmente 1 a 5 (con preferencia 1 a 3) sustituyentes en posiciones sustituibles. Como tal sustituyente, se pueden mencionar el grupo B de sustituyentes antes mencionado y el grupo oxo. Cuando se usan dos o más sustituyentes, los respectivos sustituyentes pueden ser iguales o diferentes.

Los ejemplos preferidos del "grupo acilo" incluyen

(1) grupo formilo;

(2) grupo carboxi;

(3) grupo alquil $C_{1-6}$-carbonilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) grupo alcoxi $C_{1-6}$-carbonilo,

(c) grupo arilo $C_{6-14}$ y

(d) grupo alcoxi $C_{1-6}$;

(4) grupo alcoxi $C_{1-6}$-carbonilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) grupo arilo $C_{6-14}$ y

(c) grupo alcoxi $C_{1-6}$;

(5) grupo cicloalquil $C_{3-10}$-carbonilo;

(6) grupo aril $C_{6-14}$-carbonilo opcionalmente sustituido con 1 a 3 átomos de halógeno;

(7) grupo carbamoilo opcionalmente mono- o disustituido con sustituyentes seleccionados de

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(a) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(i) átomo de halógeno,

(ii) grupo alcoxi $C_{1-6}$-carbonilo,

(iii) grupo arilo $C_{6-14}$,

(iv) grupo alcoxi $C_{1-6}$ y

(v) grupo heterocíclico aromático de 4 a 12 miembros,

(b) grupo cicloalquilo $C_{3-10}$,

(c) grupo arilo $C_{6-14}$ opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(i) átomo de halógeno,

(ii) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno y

(iii) grupo alcoxi $C_{1-6}$ y

(d) grupo heterocíclico aromático de 4 a 12 miembros;

(8) grupo alquil $C_{1-6}$-sulfonilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno y

(b) grupo arilo $C_{6-14}$;

(9) grupo aril $C_{6-14}$-sulfonilo opcionalmente sustituido con 1 a 3 átomos de halógeno;

(10) grupo sulfamoilo opcionalmente mono- o disustituido con sustituyentes seleccionados de

(a) átomo de halógeno y

(b) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de grupo heterocíclico no aromático de 4 a 12 miembros opcionalmente sustituido con grupo oxo;

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(11) grupo tiocarbamoilo opcionalmente mono- o disustituido con sustituyentes seleccionados de grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno;
(12) grupo heterociclil-carbonilo aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno;
(13) grupo heterociclil-carbonilo no aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno;
y similares.

Se explica el compuesto (I).

El anillo A es un anillo benceno opcionalmente sustituido o heterociclo aromático de 5 ó 6 miembros opcionalmente sustituido.

El heterociclo aromático de 5 ó 6 miembros para el anillo A es con preferencia piridina.

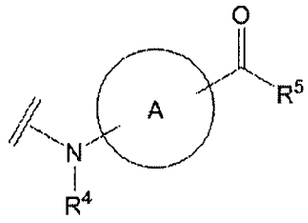
El "anillo benceno" o "heterociclo aromático de 5 ó 6 miembros" del "anillo benceno opcionalmente sustituido o heterociclo aromático de 5 ó 6 miembros opcionalmente sustituido" para el anillo A opcionalmente tiene también 1 a 4 sustituyentes en posiciones sustituibles además de "grupo -$NR^4$-" y "grupo -CO-$R^5$".

El anillo A es con preferencia un anillo benceno o heterociclo aromático de 5 ó 6 miembros (por ejemplo, piridina), con mayor preferencia benceno o un heterociclo aromático de 6 miembros (por ejemplo, piridina), con

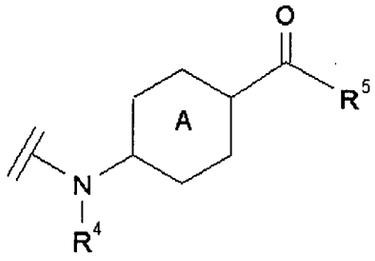
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preferencia particular, un anillo benceno, con un sustituyente distinto del "grupo $-NR^4-$" y el "grupo $-CO-R^5$".

Cuando el anillo A es benceno o un heterociclo aromático de 6 miembros, la siguiente parte que contiene el anillo A en la fórmula (I):



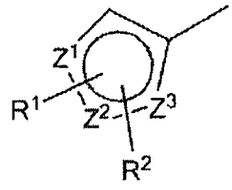

es con preferencia




en donde los símbolos distintos del anillo A son como se definieron con anterioridad.

El anillo B es pirazol.

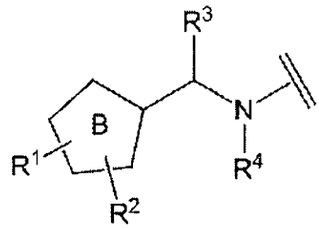
Los ejemplos específicos de pirazol para el anillo B incluyen



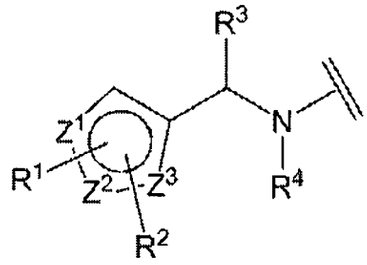

en donde $Z^1$, $Z^2$ y $Z^3$ son: 1) $Z^1$ y $Z^2$ son átomos de nitrógeno y $Z^3$ es un átomo de carbono o 2) $Z^2$ y $Z^3$ son átomos de nitrógeno y $Z^1$ es un átomo de carbono; $R^1$ y $R^2$ son como se definieron con anterioridad y estos grupos están sustituidos en cualquier posición sustituible de un anillo pirazol.

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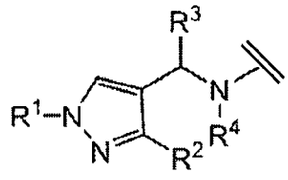
La siguiente parte que contiene el anillo B en la fórmula (I):

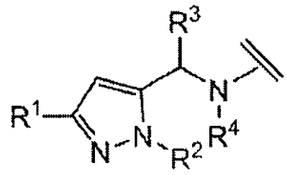


es específicamente

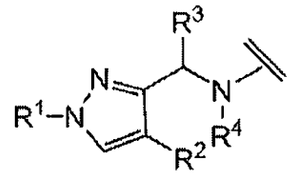


con preferencia

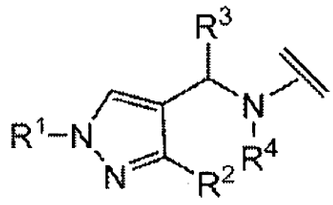




o



con mayor preferencia



en donde cada símbolo en la fórmula es como se definió con anterioridad.

$R^1$ y $R^2$ son cada uno, de modo independiente, un grupo hidrocarburo opcionalmente sustituido, un grupo heterocíclico opcionalmente sustituido, un grupo hidroxi opcionalmente sustituido o acilo.

$R^1$ es con preferencia

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(1) grupo alquilo $C_{1-6}$ opcionalmente sustituido (por ejemplo, metilo, 1,1-dimetilpropilo),

(2) grupo arilo $C_{6-14}$ opcionalmente sustituido (por ejemplo, fenilo) o

(3) grupo heterocíclico opcionalmente sustituido de 5 ó 6 miembros aromático (por ejemplo, piridilo),

con mayor preferencia

(1) grupo alquilo $C_{1-6}$ (por ejemplo, metilo, 1,1-dimetilpropilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, flúor),

(b) grupo arilo $C_{6-14}$ (por ejemplo, fenilo) y

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(2) grupo arilo $C_{6-14}$ (por ejemplo, fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, flúor, cloro),

(b) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor) y

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor) o

(3) grupo heterocíclico de 5 ó 6 miembros aromático (por ejemplo, piridilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, flúor, cloro),

(b) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor) y

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor).

$R^2$ es con preferencia

(1) grupo alquilo $C_{1-6}$ opcionalmente sustituido (por ejemplo, metilo, etilo, t-butilo, n-propilo, isopropilo),

(2) grupo hidroxi sustituido con grupo alquilo $C_{1-6}$ opcionalmente sustituido, a saber, grupo alcoxi $C_{1-6}$ opcionalmente sustituido (por ejemplo, metoxi, isopropoxi) o

(3) grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido (por ejemplo, ciclopropilo, ciclohexilo), con mayor preferencia

(1) grupo alquilo $C_{1-6}$ (por ejemplo, metilo, etilo, t-butilo, n-propilo, isopropilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, flúor, cloro),

(b) grupo arilo $C_{6-14}$ (por ejemplo, fenilo),

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) y

(d) grupo heterocíclico no aromático de 4 a 12 miembros (por ejemplo, morfolino),

(2) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, isopropoxi) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, flúor, cloro),

(b) grupo arilo $C_{6-14}$ (por ejemplo, fenilo) y

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) o

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(3) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclopropilo, ciclohexilo).

$R^3$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido, grupo arilo $C_{6-14}$ opcionalmente sustituido o grupo heterocíclico opcionalmente sustituido.

El "grupo heterocíclico opcionalmente sustituido" para $R^3$ es con preferencia un grupo heterocíclico de 5 ó 6 miembros opcionalmente sustituido.

$R^3$ es con preferencia

(1) grupo alquilo $C_{1-6}$ opcionalmente sustituido (con preferencia, grupo alquilo $C_{1-6}$ ramificado (por ejemplo, isopropilo, isobutilo, 1-etilpropilo)),

(2) grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido (por ejemplo, ciclopentilo, ciclohexilo) o

(3) grupo heterocíclico opcionalmente sustituido de 5 ó 6 miembros (por ejemplo, piridilo, piperidilo, tetrahidrotiopiranilo, 1-oxidotetrahidrotiopiranilo, 1,1-dioxidotetrahidrotiopiranilo),

con mayor preferencia

(1) grupo alquilo $C_{1-6}$ (con preferencia, grupo alquilo $C_{1-6}$ ramificado (por ejemplo, isopropilo, isobutilo, 1-etilpropilo)) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi, propoxi) opcionalmente sustituido con 1 a 3 grupos alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(b) grupo aril $C_{6-14}$-oxi (por ejemplo, feniloxi),

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(c) grupo aralquil $C_{7-13}$-oxi (por ejemplo, benciloxi),

(d) grupo amino opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ (por ejemplo, metilo),

(e) grupo heterocíclico no aromático de 4 a 12 miembros (por ejemplo, piperidilo, morfonilo),

(f) grupo alquil $C_{1-6}$-sulfonilo (por ejemplo, metilsulfonilo, isopropilsulfonilo) y

(g) grupo aril $C_{6-14}$-sulfonilo (por ejemplo, bencensulfonilo),

(2) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclohexilo) o

(3) grupo heterocíclico de 5 ó 6 miembros (por ejemplo, piridilo, piperidilo, tetrahidrotiopiranilo, 1-oxidotetrahidrotiopiranilo, 1,1-dioxidotetrahidrotiopiranilo) opcionalmente sustituido con 1 a 3 grupos arilo $C_{6-14}$ (por ejemplo, fenilo).

$R^4$ es un átomo de hidrógeno o un grupo alquilo $C_{1-6}$.

$R^4$ es con preferencia un átomo de hidrógeno.

$R^5$ es un grupo representado por $-(CH_2)_3-COOR^{11}$ o $-NR^6-CR^7R^8-CR^9R^{10}-COOR^{11}$ en donde $R^6$, $R^7$, $R^8$, $R^9$ y $R^{11}$ son cada uno, de modo independiente, un átomo de hidrógeno o un grupo alquilo $C_{1-6}$ y $R^{10}$ es un átomo de hidrógeno, un grupo alquilo $C_{1-6}$ o un grupo hidroxi.

$R^6$ es con preferencia un átomo de hidrógeno o metilo, con mayor preferencia un átomo de hidrógeno.

$R^7$ es con preferencia un átomo de hidrógeno.

$R^8$ es con preferencia un átomo de hidrógeno.

$R^9$ es con preferencia un átomo de hidrógeno, metilo o etilo, con mayor preferencia un átomo de hidrógeno.

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$R^{10}$ es con preferencia un átomo de hidrógeno, metilo o etilo, con mayor preferencia un átomo de hidrógeno.

$R^{11}$ es con preferencia un átomo de hidrógeno, metilo o etilo, con mayor preferencia un átomo de hidrógeno.

$R^5$ es con preferencia $-NR^6-CR^7R^8-CR^9R^{10}-COOR^{11}$.

De los compuestos (I), se prefiere un compuesto en donde $R^1$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, es un grupo arilo $C_{6-14}$ opcionalmente sustituido o un grupo heterocíclico aromático de 5 ó 6 miembros opcionalmente sustituido;

$R^2$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, un grupo alcoxi $C_{1-6}$ opcionalmente sustituido o es un grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido;

$R^3$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, es un grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido o un grupo heterocíclico de 5 ó 6 miembros opcionalmente sustituido;

$R^4$ es un átomo de hidrógeno;

$R^5$ es $-(CH_2)_3-COOR^{11}$ o $-NR^6-CH_2-CR^9R^{10}-COOR^{11}$;

$R^6$ es un átomo de hidrógeno o metilo;

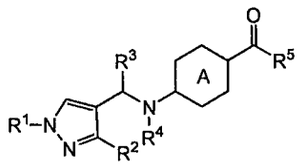
$R^9$ es un átomo de hidrógeno, metilo o etilo;

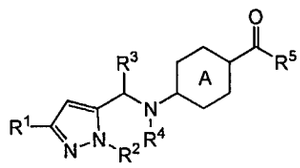
$R^{10}$ es un átomo de hidrógeno, metilo o etilo; y

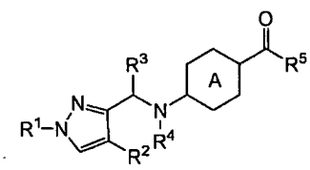
$R^{11}$ es un átomo de hidrógeno, metilo o etilo.

Cuando el anillo A es un anillo benceno o un heterociclo aromático de 6 miembros, los ejemplos preferidos específicos de la fórmula (I) incluyen las siguientes fórmulas (I'), (I") y (I"')

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(I')


(I'')


(I''')

en donde cada símbolo distinto del anillo A es como se definió con anterioridad; el compuesto representado por las fórmulas (I'), (I") y (I"') antes mencionadas y sus sales están comprendidos en el compuesto (I).

La fórmula (I) es con mayor preferencia la fórmula (I').

Los ejemplos preferidos del compuesto (I) incluyen los siguientes compuestos.

(Compuesto A)

En la fórmula (I), se prefiere un compuesto en donde el anillo A es un anillo benceno o heterociclo aromático de 5 ó 6 miembros (con preferencia, piridina);

el anillo B es pirazol;

$R^1$ es

(1) grupo alquilo $C_{1-6}$ opcionalmente sustituido (por ejemplo, metilo, 1,1-dimetilpropilo),

(2) grupo arilo $C_{6-14}$ opcionalmente sustituido (por ejemplo, fenilo) o

(3) grupo heterocíclico opcionalmente sustituido de 5 ó 6 miembros aromático (por ejemplo, piridilo);

$R^2$ es

(1) grupo alquilo $C_{1-6}$ opcionalmente sustituido (por ejemplo, metilo, etilo, t-butilo, n-propilo, isopropilo),

(2) grupo alcoxi $C_{1-6}$ opcionalmente sustituido (por ejemplo, metoxi, isopropoxi) o

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(3) grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido (por ejemplo, ciclohexilo);

$R^3$ es

(1) grupo alquilo $C_{1-6}$ opcionalmente sustituido (con preferencia, grupo alquilo $C_{1-6}$ ramificado (por ejemplo, isopropilo, isobutilo, 1-etilpropilo)),

(2) grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido (por ejemplo, ciclopropilo, ciclohexilo) o

(3) grupo heterocíclico opcionalmente sustituido de 5 ó 6 miembros (por ejemplo, piridilo, piperidilo, tetrahidrotiopiranilo, 1-oxidotetrahidrotiopiranilo, 1,1-dioxidotetrahidrotiopiranilo);

$R^4$ es un átomo de hidrógeno; y

$R^5$ es $-(CH_2)_3-COOR^{11}$ o $-NR^6-(CH_2)_2-COOR^{11}$ (con preferencia, $-NR^6-(CH_2)_2-COOR^{11}$)

en donde $R^6$ es un átomo de hidrógeno o metilo (con preferencia, un átomo de hidrógeno), y

$R^{11}$ es un átomo de hidrógeno, metilo o etilo (con preferencia, un átomo de hidrógeno);

o una de sus sales.

(Compuesto A-1)

Un compuesto de la fórmula (I), que es un compuesto de la fórmula (I') o (I") (con preferencia, fórmula (I')), en donde, el anillo A es un anillo benceno o un heterociclo aromático de 6 miembros (por ejemplo, piridina);

$R^1$ es

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(1) grupo alquilo $C_{1-6}$ (por ejemplo, metilo, 1,1-dimetilpropilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, flúor),

(b) grupo arilo $C_{6-14}$ (por ejemplo, fenilo) y

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(2) grupo arilo $C_{6-14}$ (por ejemplo, fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, flúor, cloro),

(b) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor) y

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor) o

(3) grupo heterocíclico de 5 ó 6 miembros aromático (por ejemplo, piridilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, flúor, cloro),

(b) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor) y

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor);

$R^2$ es

(1) grupo alquilo $C_{1-6}$ (por ejemplo, metilo, etilo, t-butilo, n-propilo, isopropilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

853

(a) átomo de halógeno (por ejemplo, flúor, cloro),

(b) grupo arilo $C_{6-14}$ (por ejemplo, fenilo) y

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(2) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, isopropoxi) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, flúor, cloro),

(b) grupo arilo $C_{6-14}$ (por ejemplo, fenilo) y

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) o

(3) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclopropilo, ciclohexilo);

$R^3$ es

(1) grupo alquilo $C_{1-6}$ (con preferencia, grupo alquilo $C_{1-6}$ ramificado (por ejemplo, isobutilo, 1-etilpropilo)) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi, propoxi) opcionalmente sustituido con 1 a 3 grupos alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(b) grupo aril $C_{6-14}$-oxi (por ejemplo, feniloxi),

(c) grupo aralquil $C_{7-13}$-oxi (por ejemplo, benciloxi),

(d) grupo amino opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ (por ejemplo, metilo),

(e) grupo heterocíclico no aromático de 4 a 12 miembros (por ejemplo, piperidilo, morfonilo),

(f) grupo alquil $C_{1-6}$-sulfonilo (por ejemplo, metilsulfonilo, isopropilsulfonilo) y

(g) grupo aril $C_{6-14}$-sulfonilo (por ejemplo, bencensulfonilo),

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(2) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclohexilo) o

(3) grupo heterocíclico de 5 ó 6 miembros (por ejemplo, piridilo, piperidilo, tetrahidrotiopiranilo, 1-oxidotetrahidrotiopiranilo, 1,1-dioxidotetrahidrotiopiranilo) opcionalmente sustituido con 1 a 3 grupos arilo $C_{6-14}$ (por ejemplo, fenilo);

$R^4$ es un átomo de hidrógeno; y

$R^5$ es $-(CH_2)_3-COOH$ o $-NR^6-(CH_2)_2-COOH$, con preferencia $-NR^6-(CH_2)_2-COOH$

en donde $R^6$ es un átomo de hidrógeno o metilo (con preferencia, átomo de hidrógeno));

o una de sus sales.

(Compuesto A-2)

Un compuesto de la fórmula (I), que es un compuesto de la fórmula (I'), (I") o (I"') (con preferencia, fórmula (I')),

en donde, el anillo A es un anillo benceno o un heterociclo aromático de 6 miembros (por ejemplo, piridina);

$R^1$ es

(1) grupo alquilo $C_{1-6}$ (por ejemplo, metilo, 1,1-dimetilpropilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, flúor),

(b) grupo arilo $C_{6-14}$ (por ejemplo, fenilo) y

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(2) grupo arilo $C_{6-14}$ (por ejemplo, fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, flúor, cloro),

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(b) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor) y

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor),

o

(3) grupo heterocíclico de 5 ó 6 miembros aromático (por ejemplo, piridilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, flúor, cloro),

(b) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor) y

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor);

$R^2$ es

(1) grupo alquilo $C_{1-6}$ (por ejemplo, metilo, etilo, t-butilo, n-propilo, isopropilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, flúor, cloro),

(b) grupo arilo $C_{6-14}$ (por ejemplo, fenilo),

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) y

(d) grupo heterocíclico no aromático de 4 a 12 miembros (por ejemplo, morfolino)

(2) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, isopropoxi) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

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(a) átomo de halógeno (por ejemplo, flúor, cloro),

(b) grupo arilo $C_{6-14}$ (por ejemplo, fenilo) y

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) o

(3) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclopropilo, ciclohexilo);

$R^3$ es

(1) grupo alquilo $C_{1-6}$(con preferencia, grupo alquilo $C_{1-6}$ ramificado (por ejemplo, isobutilo, 1-etilpropilo)) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi, propoxi) opcionalmente sustituido con 1 a 3 grupos alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(b) grupo aril $C_{6-14}$-oxi (por ejemplo, feniloxi),

(c) grupo aralquil $C_{7-13}$-oxi (por ejemplo, benciloxi),

(d) grupo amino opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ (por ejemplo, metilo),

(e) grupo heterocíclico no aromático de 4 a 12 miembros (por ejemplo, piperidilo, morfonilo),

(f) grupo alquil $C_{1-6}$-sulfonilo (por ejemplo, metilsulfonilo, isopropilsulfonilo) y

(g) grupo aril $C_{6-14}$-sulfonilo (por ejemplo, bencensulfonilo),

(2) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclohexilo) o

(3) grupo heterocíclico de 5 ó 6 miembros (por ejemplo, piridilo, piperidilo, tetrahidrotiopiranilo, 1-oxidotetrahidrotiopiranilo, 1,1-dioxidotetrahidrotiopiranilo) opcionalmente sustituido con 1 a 3 grupos arilo $C_{6-14}$ (por ejemplo, fenilo);

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$R^4$ es un átomo de hidrógeno; y

$R^5$ es $-(CH_2)_3-COOR^{11}$ o $-NR^6-CH_2-CR^9R^{10}-COOR^{11}$, con preferencia $-NR^6-CH_2-CR^9R^{10}-COOR^{11}$

en donde $R^6$ es un átomo de hidrógeno o metilo (con preferencia, un átomo de hidrógeno),

$R^9$ es un átomo de hidrógeno, metilo o etilo (con preferencia, un átomo de hidrógeno),

$R^{10}$ es un átomo de hidrógeno, metilo o etilo (con preferencia, un átomo de hidrógeno),

$R^{11}$ es un átomo de hidrógeno, metilo o etilo (con preferencia, un átomo de hidrógeno);

o una de sus sales.

(Compuesto A-3)

ácido 3-[({4-[(Ciclohexil{3-metil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico o una de sus sales (Ejemplo 1);

ácido 3-[{[4-({ciclohexil[1-(3-metoxifenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico o una de sus sales (Ejemplo 70); o

ácido 3-[{[4-({ciclohexil[1-(3-metoxifenil)-4-metil-1H-pirazol-3-il]metil}amino)fenil]carbonil}(metil)amino]propanoico o una de sus sales (Ejemplo 76).

El compuesto (IA) se explica a continuación.

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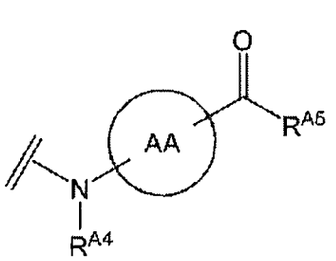
El anillo AA es un anillo benceno opcionalmente sustituido o un heterociclo aromático de 5 ó 6 miembros opcionalmente sustituido.

El heterociclo aromático de 5 ó 6 miembros para el anillo AA es con preferencia piridina.

El "anillo benceno" o "heterociclo aromático de 5 ó 6 miembros" del "anillo benceno opcionalmente sustituido o un heterociclo aromático de 5 ó 6 miembros opcionalmente sustituido" para el anillo AA opcionalmente tiene también 1 a 4 sustituyentes en posiciones sustituibles además del "grupo $-NR^{A4}-$" y "grupo $-CO-R^{A5}$".

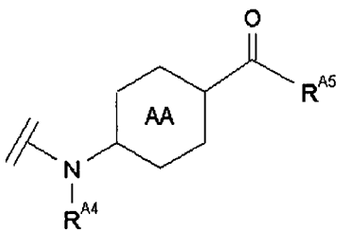
El anillo AA es con preferencia un anillo benceno o heterociclo aromático de 5 ó 6 miembros (por ejemplo, piridina), con mayor preferencia un anillo benceno o un heterociclo aromático de 6 miembros (por ejemplo, piridina), con preferencia particular, un anillo benceno, que no tiene un sustituyente además del "grupo $-NR^{A4}-$" y el "grupo $-CO-R^{A5}$".

Cuando el anillo AA es un anillo benceno o un heterociclo aromático de 6 miembros, la siguiente parte que contiene el anillo AA en la fórmula (IA)




es con preferencia

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en donde cada símbolo distinto del anillo AA es como se definió con anterioridad.

El anillo AB es un heterociclo aromático de 5 miembros opcionalmente sustituido.

El heterociclo aromático de 5 miembros para el anillo AB es con preferencia pirrol, tiofeno, furano, imidazol o pirazol.

El "heterociclo aromático de 5 miembros" del "heterociclo aromático de 5 miembros opcionalmente sustituido" para el anillo AB opcionalmente tiene también 1 ó 2 sustituyentes en posiciones sustituibles además del "grupo $-CH(R^{A3})-$".

El anillo AB es con preferencia heterociclo aromático de 5 miembros (por ejemplo, pirrol, tiofeno, furano, imidazol, pirazol, pirrol) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ (por ejemplo, metilo, etilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi) opcionalmente sustituido con 1 a 3 grupos alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(b) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclohexilo),

(c) grupo arilo $C_{6-14}$ (por ejemplo, fenilo) que opcionalmente tiene 1 a 3 grupos alquilo $C_{1-6}$ (por ejemplo, metilo)

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opcionalmente sustituidos con 1 a 3 átomos de halógeno (por ejemplo, flúor),

(d) grupo ciano,

(e) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) y

(f) átomo de halógeno (por ejemplo, átomo de bromo).

El anillo AC es un anillo benceno opcionalmente sustituido o heterociclo aromático de 5 ó 6 miembros opcionalmente sustituido.

El heterociclo aromático de 5 ó 6 miembros para el anillo AC es con preferencia piridina.

El "anillo benceno" o "heterociclo aromático de 5 ó 6 miembros" del "anillo benceno opcionalmente sustituido o heterociclo aromático de 5 ó 6 miembros opcionalmente sustituido" para el anillo AC opcionalmente tiene también 1 a 4 sustituyentes en posiciones sustituibles.

El anillo AC es con preferencia

(1) un anillo benceno opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ (por ejemplo, metilo, etilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor),

(b) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclopropilo, ciclohexilo),

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi, propoxi, isobutoxi) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(i) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(ii) grupo cicloalquilo $C_{3-6}$ (por ejemplo, ciclopropilo),

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(iii) grupo heterocíclico aromático de 4 a 12 miembros (por ejemplo, oxazolilo, isoxazolilo, piridilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de
(i') átomo de halógeno (por ejemplo, flúor, cloro) y
(ii') grupo alquilo $C_{1-6}$ (por ejemplo, metilo),
(iv) grupo heterocíclico no aromático de 4 a 12 miembros (por ejemplo, oxetanilo, tetrahidrofurilo) opcionalmente sustituido con 1 a 3 grupos alquilo $C_{1-6}$ (por ejemplo, metilo),
(v) grupo alquil $C_{1-6}$-sulfonilo (por ejemplo, metilsulfonilo),
(vi) grupo alquil $C_{1-6}$-tio (por ejemplo, metiltio) y
(vii) grupo hidroxi,
(d) átomo de halógeno (por ejemplo, flúor, cloro),
(e) grupo aralquil $C_{7-13}$-oxi (por ejemplo, benciloxi),
(f) grupo heterociclil-oxi no aromático de 4 a 12 miembros (por ejemplo, tetrahidropiraniloxi, tetrahidrotiopiraniloxi, 1,1-dioxidotetrahidrotiopiraniloxi),
(g) grupo heterociclil-oxi aromático de 4 a 12 miembros (por ejemplo, piridiloxi) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de
(i) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor) y
(ii) grupo ciano,
(h) grupo arilo $C_{6-14}$ (por ejemplo, fenilo),
(i) grupo heterocíclico aromático de 4 a 12 miembros (por ejemplo, oxazolilo, isoxazolilo, pirazolilo, piridilo)

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opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(i) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) y

(ii) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(j) grupo heterocíclico no aromático de 4 a 12 miembros (por ejemplo, morfolino, tiomorfolino),

(k) grupo aralquilo $C_{7-13}$ (por ejemplo, bencilo),

(l) grupo ciano,

(m) grupo amino opcionalmente mono- o disustituido con sustituyentes seleccionados de

(i) grupo alquilo $C_{1-6}$ (por ejemplo, metilo, etilo) opcionalmente sustituido con 1 a 3 grupos alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(ii) grupo alquil $C_{1-6}$-carbonilo (por ejemplo, acetilo),

(iii) grupo alquil $C_{1-6}$-sulfonilo (por ejemplo, metilsulfonilo),

(iv) grupo carbamoilo opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ (por ejemplo, etilo),

(v) grupo aril $C_{6-14}$-carbonilo (por ejemplo, benzoilo),

(vi) grupo aril $C_{6-14}$-sulfonilo (por ejemplo, bencensulfonilo) y

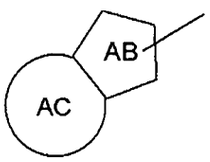
(vii) grupo aralquilo $C_{7-13}$ (por ejemplo, bencilo) y

(n) grupo aril $C_{6-14}$-sulfonilo (por ejemplo, bencensulfonilo) o

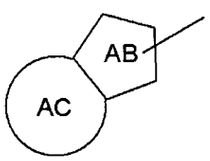
(2) heterociclo aromático de 5 ó 6 miembros (por ejemplo, piridina) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ (por ejemplo, metilo, etilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor),
(b) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclohexilo),
(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de
(i) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) y
(ii) grupo cicloalquilo $C_{3-6}$ (por ejemplo, ciclopropilo),
(d) átomo de halógeno (por ejemplo, flúor, cloro, bromo),
(e) grupo aralquil $C_{7-13}$-oxi (por ejemplo, benciloxi) y
(f) grupo heterociclil-oxi no aromático de 4 a 12 miembros (por ejemplo, tetrahidropiraniloxi).

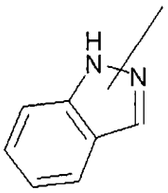
En la fórmula (IA), la parte representada por




es un grupo derivado de un anillo bicíclico formado por el anillo AB y el anillo AC que tiene un lado de cada anillo en común (es decir, condensado). Aquí, el lado del anillo AB y el lado del anillo AC incluida en la formación del anillo bicíclico están unidos en la misma multiplicidad. Por ejemplo, cuando en la fórmula (IA), la parte representada por




es un grupo representado por



,

el anillo AB es "pirazol" y el anillo AC es "benceno".

En el anillo fusionado formado por el anillo AC y el anillo AB, el "grupo $-CH(R^{A3})-$" está presente en cualquier posición unible en el anillo AB.

$R^{A3}$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido, grupo arilo $C_{6-14}$ opcionalmente sustituido o grupo heterocíclico opcionalmente sustituido.

El "grupo heterocíclico opcionalmente sustituido" para $R^{A3}$ es con preferencia un grupo heterocíclico de 5 ó 6 miembros opcionalmente sustituido.

$R^{A3}$ es con preferencia

(1) grupo alquilo $C_{1-6}$ opcionalmente sustituido (con preferencia, grupo alquilo $C_{1-6}$ ramificado (por ejemplo, isopropilo, isobutilo, 1-etilpropilo)),

(2) grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido (por ejemplo, ciclopentilo, ciclohexilo) o

(3) grupo heterocíclico opcionalmente sustituido de 5 ó 6 miembros (por ejemplo, piridilo, piperidilo, tetrahidrotiopiranilo, 1-oxidotetrahidrotiopiranilo, 1,1-dioxidotetrahidrotiopiranilo),

con mayor preferencia

(1) grupo alquilo $C_{1-6}$ (con preferencia, metilo, etilo, butilo, hexilo, grupo alquilo $C_{1-6}$ ramificado (por ejemplo,

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isopropilo, isobutilo, 1-etilpropilo)) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi, propoxi) opcionalmente sustituido con 1 a 3 grupos alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(b) grupo aril $C_{6-14}$-oxi (por ejemplo, feniloxi),

(c) grupo aralquil $C_{7-13}$-oxi (por ejemplo, benciloxi),

(d) grupo amino opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ (por ejemplo, metilo),

(e) grupo heterocíclico no aromático de 4 a 12 miembros (por ejemplo, piperidilo, morfonilo),

(f) grupo alquil $C_{1-6}$-sulfonilo (por ejemplo, metilsulfonilo, isopropilsulfonilo),

(g) grupo aril $C_{6-14}$-sulfonilo (por ejemplo, bencensulfonilo) y

(h) grupo alquil $C_{1-6}$-tio (por ejemplo, metiltio),

(2) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclopentilo, ciclohexilo),

(3) grupo heterocíclico de 5 ó 6 miembros (por ejemplo, piridilo, piperidilo, tetrahidrotiopiranilo, 1-oxidotetrahidrotiopiranilo, 1,1-dioxidotetrahidrotiopiranilo) opcionalmente sustituido con 1 a 3 grupos arilo $C_{6-14}$ (por ejemplo, fenilo) o

(4) arilo $C_{6-14}$ (por ejemplo, fenilo).

$R^{A4}$ es un átomo de hidrógeno o un grupo alquilo $C_{1-6}$.

$R^{A4}$ es con preferencia un átomo de hidrógeno.

$R^{A5}$ es un grupo representado por $-(CH_2)_3-COOR^{A11}$ o $-NR^{A6}-CR^{A7}R^{A8}-CR^{A9}R^{A10}-COOR^{A11}$, en donde $R^{A6}$, $R^{A7}$, $R^{A8}$, $R^{A9}$ y $R^{A11}$ son cada

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uno, de modo independiente, un átomo de hidrógeno o un grupo alquilo $C_{1-6}$ y $R^{A10}$ es un átomo de hidrógeno, un grupo alquilo $C_{1-6}$ o un grupo hidroxi.

$R^{A6}$ es con preferencia un átomo de hidrógeno o metilo, con mayor preferencia un átomo de hidrógeno.

$R^{A7}$ es con preferencia un átomo de hidrógeno.

$R^{A8}$ es con preferencia un átomo de hidrógeno.

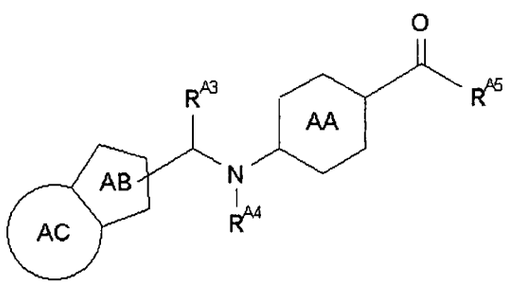
$R^{A9}$ es con preferencia un átomo de hidrógeno.

$R^{A10}$ es con preferencia un átomo de hidrógeno.

$R^{A11}$ es con preferencia un átomo de hidrógeno, metilo o etilo, con mayor preferencia un átomo de hidrógeno.

$R^{A5}$ es con preferencia $-NR^{A6}-CR^{A7}R^{A8}-CR^{A9}R^{A10}-COOR^{A11}$.

Cuando el anillo AA es un anillo benceno o un heterociclo aromático de 6 miembros, los ejemplos preferidos específicos de la fórmula (I) incluyen la siguiente fórmula (IA')




(IA')

(en donde cada símbolo distinto del el anillo AA es como se definió con anterioridad).

Un compuesto representado por la fórmula (IA') antes mencionada y una de sus sales están incluidos en el compuesto (IA).

De los compuestos representados por la fórmula (IA') antes mencionada, se prefiere un compuesto en donde

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$R^{A3}$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, es un grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido o un grupo heterocíclico de 5 ó 6 miembros opcionalmente sustituido;

$R^{A4}$ es un átomo de hidrógeno;

$R^{A5}$ es $-(CH_2)_3-COOR^{A11}$ o $-NR^{A6}-(CH_2)_2-COOR^{A11}$;

$R^{A6}$ es un átomo de hidrógeno o metilo; y

$R^{A11}$ es un átomo de hidrógeno, metilo o etilo.

Los ejemplos preferidos del compuesto (IA) incluyen los siguientes compuestos.

(Compuesto AA)

En la fórmula (IA), se prefiere un compuesto en donde el anillo AA es un anillo benceno o heterociclo aromático de 5 ó 6 miembros (por ejemplo, piridina);

el anillo AB es un heterociclo aromático de 5 miembros opcionalmente sustituido (por ejemplo, pirrol, tiofeno, furano, imidazol, pirazol);

el anillo AC es un anillo benceno opcionalmente sustituido o un heterociclo aromático de 5 ó 6 miembros opcionalmente sustituido (por ejemplo, piridina);

$R^{A3}$ es

(1) grupo alquilo $C_{1-6}$ opcionalmente sustituido (con preferencia, grupo alquilo $C_{1-6}$ ramificado (por ejemplo, isopropilo, isobutilo, 1-etilpropilo)),

(2) grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido (por ejemplo, ciclohexilo) o

(3) grupo heterocíclico opcionalmente sustituido de 5 ó 6 miembros (por ejemplo, piridilo, piperidilo,

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tetrahidrotiopiranilo, 1-oxidotetrahidrotiopiranilo, 1,1-dioxidotetrahidrotiopiranilo);

$R^{A4}$ es un átomo de hidrógeno; y

$R^{A5}$ es $-(CH_2)_3-COOR^{A11}$ o $-NR^{A6}-(CH_2)_2-COOR^{A11}$, con preferencia $-NR^{A6}-(CH_2)_2-COOR^{A11}$

en donde $R^{A6}$ es un átomo de hidrógeno o metilo (con preferencia, un átomo de hidrógeno),

$R^{A11}$ es un átomo de hidrógeno, metilo o etilo (con preferencia, un átomo de hidrógeno);

o una de sus sales.

(Compuesto AA-1)

Un compuesto de la fórmula (IA), que es un compuesto de la fórmula (IA'), en donde

el anillo AA es un anillo benceno o un heterociclo aromático de 6 miembros (por ejemplo, piridina);

el anillo AB es heterociclo aromático de 5 miembros (por ejemplo, tiofeno, furano, imidazol, pirazol) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ (por ejemplo, metilo, etilo),

(b) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclohexilo) y

(c) grupo arilo $C_{6-14}$ (por ejemplo, fenilo);

el anillo AC es

(1) un anillo benceno opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor),

(b) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclohexilo),

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) y

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(d) átomo de halógeno (por ejemplo, flúor) o

(2) heterociclo aromático de 5 ó 6 miembros (por ejemplo, piridina) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor),

(b) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclohexilo),

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) y

(d) átomo de halógeno (por ejemplo, flúor);

$R^{A3}$ es

(1) un grupo alquilo $C_{1-6}$ (con preferencia, grupo alquilo $C_{1-6}$ ramificado (por ejemplo, isobutilo, 1-etilpropilo)) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi, propoxi) opcionalmente sustituido con 1 a 3 grupos alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(b) grupo aril $C_{6-14}$-oxi (por ejemplo, feniloxi),

(c) grupo aralquil $C_{7-13}$-oxi (por ejemplo, benciloxi),

(d) grupo amino opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ (por ejemplo, metilo),

(e) grupo heterocíclico no aromático de 4 a 12 miembros (por ejemplo, piperidilo, morfonilo),

(f) grupo alquil $C_{1-6}$-sulfonilo (por ejemplo, metilsulfonilo, isopropilsulfonilo) y

(g) grupo aril $C_{6-14}$-sulfonilo (por ejemplo, bencensulfonilo),

(2) a grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclohexilo) o

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(3) grupo heterocíclico de 5 ó 6 miembros (por ejemplo, piridilo, piperidilo, tetrahidrotiopiranilo, 1-oxidotetrahidrotiopiranilo, 1,1-dioxidotetrahidrotiopiranilo) opcionalmente sustituido con 1 a 3 grupos arilo $C_{6-14}$ (por ejemplo, fenilo);

$R^{A4}$ es un átomo de hidrógeno; y

$R^{A5}$ es $-(CH_2)_3-COOH$ o $-NR^{A6}-(CH_2)_2-COOH$, con preferencia $-NR^{A6}-(CH_2)_2-COOH$

en donde $R^{A6}$ es un átomo de hidrógeno o metilo (con preferencia, un átomo de hidrógeno);

o una de sus sales.

(Compuesto AA-2)

Un compuesto de la fórmula (IA), que es un compuesto de la fórmula (IA'), en donde

el anillo AA es un anillo benceno o un heterociclo aromático de 6 miembros (por ejemplo, piridina);

el anillo AB es heterociclo aromático de 5 miembros (por ejemplo, tiofeno, furano, imidazol, pirazol) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ (por ejemplo, metilo, etilo) opcionalmente sustituido con 1 a 3 grupos alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(b) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclohexilo) y

(c) grupo arilo $C_{6-14}$ (por ejemplo, fenilo);

el anillo AC es

(1) un anillo benceno opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

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(a) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor),
(b) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclohexilo),
(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de
(i) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) y
(ii) grupo cicloalquilo $C_{3-6}$ (por ejemplo, ciclopropilo),
(d) átomo de halógeno (por ejemplo, flúor),
(e) grupo aralquil $C_{7-13}$-oxi (por ejemplo, benciloxi) y
(f) grupo heterociclil-oxi no aromático de 4 a 12 miembros (por ejemplo, tetrahidropiraniloxi) o
(2) heterociclo aromático de 5 ó 6 miembros (por ejemplo, piridina) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de
(a) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor),
(b) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclohexilo),
(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de
(i) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) y
(ii) grupo cicloalquilo $C_{3-6}$ (por ejemplo, ciclopropilo),
(d) átomo de halógeno (por ejemplo, flúor),
(e) grupo aralquil $C_{7-13}$-oxi (por ejemplo, benciloxi) y
(f) grupo heterociclil-oxi no aromático de 4 a 12 miembros (por ejemplo, tetrahidropiraniloxi);
$R^{A3}$ es

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(1) grupo alquilo $C_{1-6}$ (con preferencia, grupo alquilo $C_{1-6}$ ramificado (por ejemplo, isopropilo, isobutilo, 1-etilpropilo)) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi, propoxi) opcionalmente sustituido con 1 a 3 grupos alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(b) grupo aril $C_{6-14}$-oxi (por ejemplo, feniloxi),

(c) grupo aralquil $C_{7-13}$-oxi (por ejemplo, benciloxi),

(d) grupo amino opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ (por ejemplo, metilo),

(e) grupo heterocíclico no aromático de 4 a 12 miembros (por ejemplo, piperidilo, morfonilo),

(f) grupo alquil $C_{1-6}$-sulfonilo (por ejemplo, metilsulfonilo, isopropilsulfonilo) y

(g) grupo aril $C_{6-14}$-sulfonilo (por ejemplo, bencensulfonilo),

(2) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclopentilo, ciclohexilo) o

(3) grupo heterocíclico de 5 ó 6 miembros (por ejemplo, piridilo, piperidilo, tetrahidrotiopiranilo, 1-oxidotetrahidrotiopiranilo, 1,1-dioxidotetrahidrotiopiranilo) opcionalmente sustituido con 1 a 3 grupos arilo $C_{6-14}$ (por ejemplo, fenilo);

$R^{A4}$ es un átomo de hidrógeno; y

$R^{A5}$ es $-(CH_2)_3-COOR^{A11}$ o $-NR^{A6}-(CH_2)_2-COOR^{A11}$, con preferencia $-NR^{A6}-(CH_2)_2-COOR^{A11}$

en donde $R^{A6}$ es un átomo de hidrógeno o metilo (con preferencia, un átomo de hidrógeno) y $R^{A11}$ es un átomo de

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hidrógeno, metilo o etilo (con preferencia, un átomo de hidrógeno));

o una de sus sales.

(Compuesto AA-3)

Un compuesto de la fórmula (IA), que es un compuesto de la fórmula (IA'), en donde

el anillo AA es un anillo benceno o un heterociclo aromático de 6 miembros (por ejemplo, piridina);

el anillo AB es un heterociclo aromático de 5 miembros (por ejemplo, pirrol, tiofeno, furano, imidazol, pirazol, pirrol) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ (por ejemplo, metilo, etilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi) opcionalmente sustituido con 1 a 3 grupos alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(b) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclohexilo),

(c) grupo arilo $C_{6-14}$ (por ejemplo, fenilo) que opcionalmente tiene 1 a 3 grupos alquilo $C_{1-6}$ (por ejemplo, metilo) opcionalmente sustituidos con 1 a 3 átomos de halógeno (por ejemplo, flúor),

(d) grupo ciano,

(e) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) y

(f) átomo de halógeno (por ejemplo, átomo de bromo);

el anillo AC es

(1) anillo benceno opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

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(a) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor),
(b) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclopropilo, ciclohexilo),
(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi, propoxi, isobutoxi) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de
(i) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi),
(ii) grupo cicloalquilo $C_{3-6}$ (por ejemplo, ciclopropilo),
(iii) grupo heterocíclico aromático de 4 a 12 miembros (por ejemplo, oxazolilo, isoxazolilo, piridilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de
(i') átomo de halógeno (por ejemplo, flúor, cloro) y
(ii') grupo alquilo $C_{1-6}$ (por ejemplo, metilo),
(iv) grupo heterocíclico no aromático de 4 a 12 miembros (por ejemplo, oxetanilo, tetrahidrofurilo) opcionalmente sustituido con 1 a 3 grupos alquilo $C_{1-6}$ (por ejemplo, metilo),
(v) grupo alquil $C_{1-6}$-sulfonilo (por ejemplo, metilsulfonilo),
(vi) grupo alquil $C_{1-6}$-tio (por ejemplo, metiltio) y
(vii) grupo hidroxi,
(d) átomo de halógeno (por ejemplo, flúor, cloro),
(e) grupo aralquil $C_{7-13}$-oxi (por ejemplo, benciloxi),
(f) grupo heterociclil-oxi no aromático de 4 a 12 miembros (por ejemplo, tetrahidropiraniloxi, tetrahidrotiopiraniloxi, 1,1-dioxidotetrahidrotiopiraniloxi),

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(g) grupo heterociclil-oxi aromático de 4 a 12 miembros (por ejemplo, piridiloxi) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(i) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor) y

(ii) grupo ciano,

(h) grupo arilo $C_{6-14}$ (por ejemplo, fenilo),

(i) grupo heterocíclico aromático de 4 a 12 miembros (por ejemplo, oxazolilo, isoxazolilo, pirazolilo, piridilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(i) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) y

(ii) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(j) grupo heterocíclico no aromático de 4 a 12 miembros (por ejemplo, morfolino, tiomorfolino),

(k) grupo aralquilo $C_{7-13}$ (por ejemplo, bencilo),

(l) grupo ciano,

(m) grupo amino opcionalmente mono- o disustituido con sustituyentes seleccionados de

(i) grupo alquilo $C_{1-6}$ (por ejemplo, metilo, etilo) opcionalmente sustituido con 1 a 3 grupos alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(ii) grupo alquil $C_{1-6}$-carbonilo (por ejemplo, acetilo),

(iii) grupo alquil $C_{1-6}$-sulfonilo (por ejemplo, metilsulfonilo),

(iv) grupo carbamoilo opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ (por ejemplo, etilo),

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(v) grupo aril $C_{6-14}$-carbonilo (por ejemplo, benzoilo),

(vi) grupo aril $C_{6-14}$-sulfonilo (por ejemplo, bencensulfonilo)

y

(vii) grupo aralquilo $C_{7-13}$ (por ejemplo, bencilo) y

(n) grupo aril $C_{6-14}$-sulfonilo (por ejemplo, bencensulfonilo)

o

(2) heterociclo aromático de 5 ó 6 miembros (por ejemplo, piridina) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) grupo alquilo $C_{1-6}$ (por ejemplo, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (por ejemplo, flúor),

(b) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclohexilo),

(c) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(i) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi) y

(ii) grupo cicloalquilo $C_{3-6}$ (por ejemplo, ciclopropilo),

(d) átomo de halógeno (por ejemplo, flúor, cloro, bromo),

(e) grupo aralquil $C_{7-13}$-oxi (por ejemplo, benciloxi) y

(f) grupo heterociclil-oxi no aromático de 4 a 12 miembros (por ejemplo, tetrahidropiraniloxi);

$R^{A3}$ es

(1) grupo alquilo $C_{1-6}$ (con preferencia, metilo, etilo, butilo, hexilo, grupo alquilo $C_{1-6}$ ramificado (por ejemplo, isopropilo, isobutilo, 1-etilpropilo)) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

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(a) grupo alcoxi $C_{1-6}$ (por ejemplo, metoxi, etoxi, propoxi) opcionalmente sustituido con 1 a 3 grupos alcoxi $C_{1-6}$ (por ejemplo, metoxi),

(b) grupo aril $C_{6-14}$-oxi (por ejemplo, feniloxi),

(c) grupo aralquil $C_{7-13}$-oxi (por ejemplo, benciloxi),

(d) grupo amino opcionalmente mono- o disustituido con el grupo alquilo $C_{1-6}$ (por ejemplo, metilo),

(e) grupo heterocíclico no aromático de 4 a 12 miembros (por ejemplo, piperidilo, morfonilo),

(f) grupo alquil $C_{1-6}$-sulfonilo (por ejemplo, metilsulfonilo, isopropilsulfonilo),

(g) grupo aril $C_{6-14}$-sulfonilo (por ejemplo, bencensulfonilo) y

(h) grupo alquil $C_{1-6}$-tio (por ejemplo, metiltio),

(2) grupo cicloalquilo $C_{3-10}$ (por ejemplo, ciclopentilo, ciclohexilo),

(3) grupo heterocíclico de 5 ó 6 miembros (por ejemplo, piridilo, piperidilo, tetrahidrotiopiranilo, 1-oxidotetrahidrotiopiranilo, 1,1-dioxidotetrahidrotiopiranilo) opcionalmente sustituido con 1 a 3 grupos arilo $C_{6-14}$ (por ejemplo, fenilo) o

(4) arilo $C_{6-14}$ (por ejemplo, fenilo);

$R^{A4}$ es un átomo de hidrógeno; y

$R^{A5}$ es $-(CH_2)_3-COOR^{A11}$ o $-NR^{A6}-(CH_2)_2-COOR^{A11}$, con preferencia, $-NR^{A6}-(CH_2)_2-COOR^{A11}$

en donde $R^{A6}$ es un átomo de hidrógeno o metilo (con preferencia, un átomo de hidrógeno) y $R^{A11}$ es un átomo de

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hidrógeno, metilo o etilo (con preferencia, un átomo de hidrógeno);

o una de sus sales.

(Compuesto AA-4)

ácido 3-{[(4-{[Ciclohexil(3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico o una de sus sales (Ejemplo A41);

ácido 3-{[(6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil](metil)amino}propanoico o una de sus sales Ejemplo A53);

ácido 3-{[(4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil](metil)amino}propanoico o una de sus sales (Ejemplo A73);

ácido 3-[{[4-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico o una de sus sales (Ejemplo A78); o

ácido 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico o una de sus sales (Ejemplo A83).

Como sales de los compuestos (I) y (IA), se prefieren las sales farmacológicamente aceptables correspondientes. Los ejemplos de dicha sal incluyen una sal con una base inorgánica, una sal con una base orgánica, una sal con un ácido inorgánico, una sal con un ácido orgánico, una sal con aminoácidos ácidos o básicos y similares.

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Los ejemplos de preferencia de una sal con una base inorgánica incluyen sales de metales alcalinos tales como sal de sodio, sal de potasio y similares; sales de metales alcalinotérreos tales como sal de calcio, sal de magnesio y similares; sal de aluminio; sal de amonio y similares.

Los ejemplos de preferencia de la sal con la base orgánica incluyen sales con trimetilamina, trietilamina, piridina, picolina, etanolamina, dietanolamina, trietanolamina, trometamina [tris(hidroximetil)metilamina], ter-butilamina, ciclohexilamina, bencilamina, diciclohexilamina, N,N-dibenciletilendiamina y similares.

Los ejemplos de preferencia de la sal con ácido inorgánico incluyen las sales con ácido clorhídrico, ácido bromhídrico, ácido nítrico, ácido sulfúrico, ácido fosfórico, y similares.

Los ejemplos de preferencia de la sal con ácido orgánico incluyen las sales con ácido fórmico, ácido acético, ácido trifluoroacético, ácido ftálico, ácido fumárico, ácido oxálico, ácido tartárico, ácido maleico, ácido cítrico, ácido succínico, ácido málico, ácido metanosulfónico, ácido bencenosulfónico, ácido p-toluenosulfónico y similares.

Los ejemplos de preferencia de la sal con aminoácido básico incluyen sales con arginina, lisina, ornitina y similares.

Los ejemplos de preferencia de la sal con aminoácido ácido incluyen sales con ácido aspártico, ácido glutámico y similares.

El término profármaco del compuesto (I) o (IA) significa un compuesto que es convertido en el compuesto (I) o (IA) en la condición fisiológica del organismo viviente por una reacción con una enzima, un ácido gástrico o similares, es decir, por oxidación, reducción, hidrólisis enzimática, etc.; por hidrólisis con ácido gástrico, etc.

Los ejemplos de los profármacos del compuesto (I) y compuesto (IA) incluyen un compuesto obtenido al someter un grupo amino en el compuesto (I) y el compuesto (IA) a una acilación, alquilación o fosforilación (por ejemplo, un compuesto obtenido al someter un grupo amino en el compuesto (I) y el compuesto (IA) a una eicosanoilación, alanilación, pentilaminocarbonilación, (5-metil-2-oxo-1,3-dioxolen-4-il)metoxicarbonilación, tetrahidrofuranoilación, pirrolidilmetilación, pivaloiloximetilación o ter-butilación); un compuesto obtenido al someter un grupo hidroxi en el compuesto (I) y el compuesto (IA) a una acilación, alquilación, fosforilación o boración (por ejemplo, un compuesto obtenido al someter un grupo hidroxi en el compuesto (I) y el compuesto (IA) a una acetilación, palmitoilación, propanoilación, pivaloilación, succinilación, fumarilación, alanilación o dimetilaminometilcarbonilación); un compuesto obtenido al someter un grupo carboxilo en el compuesto (I) y el compuesto (IA) a una esterificación o amidación (por ejemplo, un compuesto obtenido al someter un grupo carboxilo en el compuesto (I) y el compuesto (IA) a una etilesterificación, fenilesterificación, carboximetilesterificación, dimetilaminometilesterificación,

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pivaloiloximetilesterificación, etoxicarboniloxietilesterificación, ftalidilesterificación, (5-metil-2-oxo-1,3-dioxolen-4-il)metilesterificación, ciclohexiloxicarboniletilesterificación o metilamidación etc.) y similares. Estos compuestos se pueden producir a partir del compuesto (I) y el compuesto (IA) de acuerdo con un método conocido *per se*.

Un profármaco del compuesto (I) y el compuesto (IA) también puede ser uno que es convertido en el compuesto (I) y el compuesto (IA) en una condición fisiológica, tal como las descritas en el documento IYAKUHIN no KAIHATSU, Development de Pharmaceuticals, Vol. 7, Design of Molecules, p. 163-198, Publicado por HIROKAWA SHOTEN, 1990.

Los compuestos (I) y (IA) y sus profármacos correspondientes (en ocasiones abreviados colectivamente como "el compuesto de la presente invención" en la presente memoria descriptiva) incluyen estereoisómeros tales como isómeros cis, trans y similares, formas óptimamente activas tales como racematos, compuestos R y compuestos S y similares. Según el tipo de anillo tal como anillo A y similares, los isómeros se pueden producir por conformación y dichos isómeros también se incluyen en el compuesto de la presente invención.

El compuesto de la presente invención se puede rotular con un isótopo (por ejemplo, $^{2}H$, $^{3}H$, $^{14}C$, $^{35}S$, $^{125}I$) y similares. El compuesto de la presente invención puede ser un hidrato, no hidrato, solvato o no solvato.

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El compuesto de la presente invención tiene baja toxicidad y se puede usar como agente para la profilaxis o el tratamiento de diversas enfermedades mencionadas más adelante en un mamífero (por ejemplo, humano, ratón, rata, conejo, perro, gato, bovino, caballo, cerdo, mono) directamente o en la forma de una composición farmacéutica al mezclarlo con un portador farmacéuticamente aceptable y similares.

Aquí, los ejemplos de los portadores farmacéuticamente aceptables incluyen diversas sustancias portadoras orgánicas o inorgánicas usadas convencionalmente como excipiente, lubricante, aglutinante o desintegrante para las formas de dosificación sólida; como solvente, agente solubilizante, agente de suspensión, agente de isotonicidad, agente amortiguador o suavizante para la preparación líquida, y similares. De ser necesario, también se pueden usar aditivos de la preparación tales como conservadores, antioxidantes, colorantes, edulcorantes y similares.

Los ejemplos preferidos de excipientes incluyen lactosa, sacarosa, D-manitol, D-sorbitol, almidón, almidón pregelatinizado, dextrina, celulosa cristalina, hidroxipropilcelulosa poco sustituida, carboximetilcelulosa de sodio, goma arábiga, pululano, ácido silícico anhidro liviano, silicato de aluminio sintético y aluminometasilicato de magnesio.

Los ejemplos preferidos de lubricante incluyen estearato de magnesio, estearato de calcio, talco y sílice coloidal.

Los ejemplos preferidos de aglutinante incluyen almidón pregelatinizado, sacarosa, gelatina, goma arábiga,

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metilcelulosa, carboximetilcelulosa, carboximetilcelulosa de sodio, celulosa cristalina, sacarosa, D-manitol, trehalosa, dextrina, pululano, hidroxipropilcelulosa, hidroxipropilmetilcelulosa y polivinilpirrolidona.

Los ejemplos preferidos de desintegrante incluyen lactosa, sacarosa, almidón, carboximetilcelulosa, carboximetilcelulosa de calcio, croscarmelosa de sodio, carboximetilalmidón de sodio, ácido silícico anhidro liviano e hidroxipropilcelulosa poco sustituida.

Los ejemplos preferidos de solvente incluyen agua para inyección, salmuera fisiológica, solución de Ringer, alcohol, propilenglicol, polietilenglicol, aceite de sésamo, aceite de maíz, aceite de oliva y aceite de semilla de algodón.

Los ejemplos preferidos de agente solubilizante incluyen polietilenglicol, propilenglicol, D-manitol, trehalosa, benzoato de bencilo, etanol, trisaminometano, colesterol, trietanolamina, carbonato de sodio, citrato de sodio, salicilato de sodio y acetato de sodio.

Los ejemplos preferidos de agente de suspensión incluyen agentes tensioactivos tales como estearíltrietanolamina, laurilsulfato de sodio, ácido laurilaminopropiónico, lecitina, cloruro de benzalconio, cloruro de bencetonio, monoestearato de glicerilo y similares; polímeros hidrofílicos tales como alcohol polivinílico, polivinilpirrolidona, carboximetilcelulosa de sodio, metilcelulosa, hidroximetilcelulosa, hidroxietilcelulosa, hidroxipropilcelulosa y similares; polisorbatos y aceite de ricino hidrogenado con polioxietileno.

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Los ejemplos preferidos de agente de isotonicidad incluyen cloruro de sodio, glicerol, D-manitol, D-sorbitol y glucosa.

Los ejemplos preferidos de amortiguador incluyen amortiguadores tales como fosfato, acetato, carbonato, citrato y similares.

Los ejemplos preferidos de agente suavizante incluyen alcohol bencílico.

Los ejemplos preferidos de conservante incluyen paraoxibenzoatos, clorobutanol, alcohol bencílico, alcohol fenetílico, ácido deshidroacético y ácido sórbico.

Los ejemplos preferidos de antioxidante incluyen sulfito, ascorbato y similares.

Los ejemplos preferidos de colorante incluyen colores de alquitrán alimenticios acuosos (por ejemplo, colores alimenticios tales como Food Red No. 2 y No. 3, Food Yellow No. 4 y No. 5, Food Blue No. 1 y No. 2, etc.), colorantes de laca insolubles en agua (por ejemplo, sal de aluminio de los colores de alquitrán alimenticios acuosos antes mencionados) y colorantes naturales (por ejemplo, β-caroteno, clorofila, óxido de hierro rojo).

Los ejemplos preferidos de agente edulcorante incluyen sacarina de sodio, glicirrizinato de dipotasio, aspartamo y estevia.

Los ejemplos de la forma de dosificación de la composición farmacéutica antes mencionada incluyen preparaciones orales tales como comprimidos (inclusive de comprimidos recubiertos de azúcar, comprimidos recubiertos de

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película, comprimidos sublinguales, comprimidos de desintegración oral), cápsulas (inclusive de cápsulas blandas, microcápsulas), gránulos, polvos, grageas, jarabes, emulsiones, suspensiones, películas (por ejemplo, películas orales desintegrables) y similares; y agentes parenterales tales como inyecciones (por ejemplo, inyecciones subcutáneas, inyecciones intravenosas, inyecciones intramusculares, inyecciones intraperitoneales, infusiones por goteo), preparaciones externas (por ejemplo, preparaciones dérmicas, ungüentos), supositorios (por ejemplo, supositorios rectales, supositorios vaginales), pellets, preparaciones nasales, preparaciones pulmonares (inhalantes), gotas oculares y similares. Estas se pueden administrar con seguridad por las vías oral o parenteral (por ejemplo, las administraciones tópica, rectal, intravenosa).

Estas preparaciones pueden ser preparaciones de liberación controlada (por ejemplo, microcápsulas de liberación sostenida) tales como preparación de liberación inmediata, preparación de liberación sostenida, y similares.

Una composición farmacéutica se puede producir por un método convencionalmente usado en el campo técnico de la preparación farmacéutica, por ejemplo, el método descrito en la Farmacopea japonesa y similares.

Si bien el contenido del compuesto de la presente invención en la composición farmacéutica varía según la forma de dosificación, la dosis del compuesto de la presente invención y similares, es, por ejemplo, de aproximadamente 0,1 a 100 % en peso.

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Durante la producción de una preparación oral, se puede aplicar un recubrimiento según sea necesario con el fin de enmascarar el sabor, la propiedad entérica o la durabilidad.

Los ejemplos de la base de recubrimiento que se usan para cobertura incluyen base de recubrimiento de azúcar, base de recubrimiento de película acuosa, base de recubrimiento de película entérica y base de recubrimiento de película de liberación sostenida.

Como base de recubrimiento de azúcar, se usa sacarosa. Además, se puede usar uno o más tipos seleccionados de talco, carbonato de calcio precipitado, gelatina, goma arábiga, pululano, cera de carnauba y similares en combinación.

Los ejemplos de base de recubrimiento de película acuosa incluyen polímeros de celulosa tales como hidroxipropilcelulosa, hidroxipropilmetilcelulosa, hidroxietilcelulosa, metilhidroxietilcelulosa, etc.; polímeros sintéticos tales como dietilaminoacetato de polivinilacetal, copolímero E de aminoalquilmetacrilato [Eudragit E (nombre comercial)], polivinilpirrolidona etc.; y polisacáridos tales como pululano, etc.

Los ejemplos de base de recubrimiento de película entérica incluyen polímeros de celulosa tales como ftalato de hidroxipropilmetilcelulosa, acetato-succinato de hidroxipropilmetilcelulosa, carboximetiletilcelulosa, acetato-ftalato de celulosa, etc.; polímeros acrílicos tales como copolímero L de ácido metacrílico [Eudragit L (nombre comercial)], copolímero LD de ácido metacrílico [Eudragit L-30D55 (nombre comercial)], copolímero S de ácido metacrílico

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[Eudragit S (nombre comercial)], etc.; y sustancias que aparecen en la naturaleza tales como lacas, etc.

Los ejemplos de base de recubrimiento de película de liberación sostenida incluyen polímeros de celulosa tales como etilcelulosa, etc.; y polímeros de acrílico tales como copolímero RS de aminoalquilmetacrilato [Eudragit RS (nombre comercial)], copolímero-suspensión de acrilato de etilo-metacrilato de metilo [Eudragit NE (nombre comercial)], etc.

Las bases de recubrimiento antes mencionadas se pueden usar después de mezcladas con dos o más tipos de ellas en las proporciones adecuadas. Para el recubrimiento se puede usar, por ejemplo, un agente protector liviano tal como óxido de titanio, trióxido de dihierro y similares.

El compuesto de la presente invención muestra baja toxicidad (por ejemplo, toxicidad aguda, toxicidad crónica, toxicidad genética, toxicidad reproductiva, cardiotoxicidad, carcinogenicidad y similares) y escasos efectos secundarios. En consecuencia, se puede usar como agente para la profilaxis o el tratamiento o un diagnóstico de diversas enfermedades en un mamífero (por ejemplo, humano, bovino, caballo, perro, gato, mono, ratón, rata).

El compuesto de la presente invención tiene superior acción antagonista de glucagón.

El compuesto de la presente invención puede mejorar el estado que incluye promover la función del glucagón (por ejemplo, exceso de producción de azúcar por parte del hígado, exceso de secreción de hormona del crecimiento, exceso de supresión de la motilidad gástrica, y similares), por

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ejemplo, al cortar la acción del glucagón. En consecuencia, el compuesto de la presente invención puede ser útil como antagonista de glucagón, un agente supresor de la producción de azúcar, un agente preventivo o terapéutico para enfermedades que incluyen la promoción de la acción de glucagón y similares.

Específicamente, el compuesto de la presente invención se puede usar como agente preventivo o terapéutico para obesidad, diabetes (por ejemplo, diabetes tipo 1, diabetes tipo 2, diabetes gestacional, diabetes del obeso), hiperlipidemia (por ejemplo, hipertrigliceridemia, hipercolesterolemia, hipoHDL-emia, hiperlipemia posprandial), hipertensión, insuficiencia cardiaca, complicaciones diabéticas [por ejemplo, neuropatía, nefropatía, retinopatía, cardiomiopatía diabética, cataratas, macroangiopatía, osteopenia, coma diabético hiperosmolar, infecciones (por ejemplo, infección respiratoria, infección de vías urinarias, infección gastrointestinal, infecciones de los tejidos blandos dérmicos, infección de miembros inferiores), gangrena diabética, xerostomía con hipacusia, hipacusia, trastorno cerebrovascular, trastorno de la circulación de sangre periférica], síndrome metabólico (patología que contiene tres o más seleccionados de hiper-triglicerid(TG)emia, hipo-HDL-colesterol (HDL-C)emia, hipertensión, obesidad abdominal y deterioro de la tolerancia a la glucosa), sarcopenia y similares.

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Para los criterios de diagnóstico de diabetes, la Sociedad de Diabetes de Japón informó nuevos criterios de diagnóstico en 1999.

De acuerdo con este informe, la diabetes es una condición que muestra cualquiera de un nivel de glucosa sanguínea en ayunas (concentración de glucosas de plasma intravenoso) no inferior a 126 mg/dl, un nivel de prueba de tolerancia a 75 g de glucosa oral (75 g OGTT) a las 2 h (concentración de glucosa en plasma intravenoso) no inferior a 200 mg/dl y un nivel de glucosa sanguínea no en ayunas (concentración de glucosa en plasma intravenoso) no inferior a 200 mg/dl. Una condición no incluida en la diabetes antes mencionada y diferente de "una condición que presenta un nivel de glucosa sanguínea en ayunas (concentración de glucosa en plasma intravenoso) inferior a 110 mg/dl o un nivel de prueba de tolerancia a 75 g de glucosa oral (75 g OGTT) a las 2 h (concentración de glucosa en plasma intravenoso) inferior a 140 mg/dl" (tipo normal) se denomina "tipo *borderline*".

Además, la ADA (American Diabetes Association) en 1997 y la OMS en 1998 informaron nuevos criterios de diagnóstico de diabetes.

De acuerdo con estos informes, la diabetes es una condición que presenta un nivel de glucosa sanguínea en ayunas (concentración de glucosa en plasma intravenoso) no inferior a 126 mg/dl y un nivel de prueba de tolerancia a 75 g de glucosa oral (concentración de glucosa en plasma intravenoso) no inferior a 200 mg/dl.

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De acuerdo con los informes antes mencionados, deterioro de tolerancia de glucosa es una condición que presenta un nivel de glucosa sanguínea en ayunas (concentración de glucosa en plasma intravenoso) inferior a 126 mg/dl y un nivel de prueba de tolerancia a 75 g de glucosa oral (concentración de glucosa en plasma intravenoso) no inferior a 140 mg/dl e inferior a 200 mg/dl. De acuerdo con el informe de ADA, una condición que presenta un nivel de glucosa sanguínea en ayunas (concentración de glucosa en plasma intravenoso) no inferior a 110 mg/dl e inferior a 126 mg/dl se denomina IFG (Deterioro de glucosa en ayunas). De acuerdo con el informe de la OMS, entre las IFG (Deterioro de glucosa en ayunas), una condición que presenta un nivel de prueba de tolerancia a 75 g de glucosa oral (concentración de glucosa en plasma intravenoso) inferior a 140 mg/dl se denomina IFG (Deterioro de glucemia en ayunas).

El compuesto de la presente invención también se puede usar como agente para la profilaxis o el tratamiento de diabetes, de tipo *borderline*, deterioro de tolerancia de glucosa, IFG (Deterioro de glucosa en ayunas) e IFG (Deterioro de glucemia en ayunas), tal como se determinó de acuerdo con los nuevos criterios de diagnóstico antes mencionados. Además, el compuesto de la presente invención puede prevenir el progreso del tipo *borderline*, el deterioro de tolerancia de glucosa, IFG (Deterioro de glucosa en ayunas) o IFG (Deterioro de glucemia en ayunas) a diabetes.

Además, el compuesto de la presente invención también se puede usar como agente preventivo o terapéutico para

osteoporosis, caquexia (por ejemplo, carcinocaquexia, caquexia tuberculosa, caquexia diabética, caquexia hemopática, caquexia endocrinopática, caquexia infecciosa, caquexia en enfermedad cardiaca o caquexia inducida por síndrome de inmunodeficiencia adquirida), hígado graso, síndrome de ovario poliquístico, enfermedades renales (por ejemplo, nefropatía diabética, glomerulonefritis, glomeruloesclerosis, síndrome de nefrosis, nefroesclerosis hipertensiva, trastorno renal de estadio terminal), distrofia muscular, infarto de miocardio, angina pectoris, trastorno cerebrovascular (por ejemplo, infarto cerebral, apoplejía cerebral), isquemia, coronariopatía, infarto de miocardio no de onda Q (IM no de onda Q), insuficiencia cardiaca congestiva, hipertrofia ventricular, arritmia cardiaca, claudicación intermitente, enfermedad obstructiva de arterias periféricas (por ejemplo, trastorno arterial periférico), enfermedad de Alzheimer, enfermedad de Parkinson, ansiedad, demencia, síndrome de resistencia a insulina, síndrome X, hiperinsulinemia, trastorno de percepción en hiperinsulinemia, tumores (por ejemplo, leucemia, cáncer de mama, cáncer de próstata, cáncer de piel, cáncer epitelial, cáncer glandular), síndrome de intestino irritable, diarrea aguda o crónica, enfermedad inflamatoria (por ejemplo, artritis reumatoidea crónica, espondilitis deformante, osteoartritis, lumbago, gota, artritis gotosa, inflamación posterior a cirugía o traumatismo, tumefacción, neuralgia, faringolaringitis, cistitis, hepatitis (incluso esteatohepatitis no alcohólica), neumonía, pancreatitis,

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enteritis, enfermedad inflamatoria intestinal (incluso colitis inflamatoria), colitis ulcerativa, lesión de la mucosa gástrica (incluso lesión de la mucosa gástrica causada por aspirina), enfermedad de Lyme, artritis por rubéola, artritis psoriásica, conjuntivitis, gastritis, tiroiditis crónica, hepatitis crónica activa, enfermedad de Crohn, sinovitis, espondilitis anquilosante), lesión de la mucosa del intestino delgado, malabsorción, disfunción testicular, síndrome de obesidad visceral, sarcopenia, degeneración macular, anemia hipoplásica, trombocitopenia, esclerosis múltiple, enfermedad periodontal, formación de queloide, sarcoidosis pulmonar, miastenia gravis, síndrome de Reiter, influenza, malaria cerebral, silicosis, enfermedad de resorción ósea, fiebre, dolor muscular, enfermedades óseas relacionadas con mieloma múltiple, enfermedades neurodegenerativas debidas a traumatismo, lesión cerebral traumática, gigantismo, reacción injerto versus huésped, rechazo de trasplante, condición patológica cutánea (por ejemplo, formación de tejido cicatrizal, eczema, dermatitis atópica, dermatitis por contacto, urticaria, esclerodermia, psoriasis), alergia o enfermedades respiratorias (por ejemplo, asma, síndrome de distrés respiratorio, fiebre de heno, rinitis alérgica, enfermedad pulmonar inflamatoria crónica (por ejemplo, enfermedades pulmonares obstructiva crónica (EPOC)), inflamación relacionada con enfermedades autoinmunes (por ejemplo, lupus eritematoso sistémico, enfermedad de Addison, síndrome de deficiencia poliglandular, enfermedad de Graves, enfermedad infecciosa (por ejemplo,

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sepsis, shock séptico, shigellosis, por *Helicobacter pylori*), enfermedad viral (por ejemplo, infección por virus herpes simple, infección por citomegalovirus, infección por virus de Epstein-Barr, infección por virus de inmunodeficiencia humana, infección por virus de hepatitis tipo A, tipo B y tipo C, enfermedad angiogenética (por ejemplo, tumores sólidos, neovasculización ocular, hemangioma, edema, analgesia, dolor (por ejemplo, dolor neuromuscular, cefalea, dolor causado por cáncer o cirugía, dolor de muelas, dolor artrítico), síndrome de intestino irritable, leucemia, enfermedades del sistema nervioso central (por ejemplo, debido a isquemia cerebral, infarto cerebral, edema cerebral y similares), fibrosis renal, fibrosis hepática, fibrosis de próstata, fibrosis pulmonar y similares.

Además, el compuesto de la presente invención también se puede usar como mejorador de la función de motilidad gastrointestinal.

El compuesto de la presente invención también se puede usar para la prevención secundaria y la supresión de la progresión (por ejemplo, la prevención secundaria y la supresión de la progresión de eventos cardiovasculares tales como infarto de miocardio y similares) de las diversas enfermedades antes mencionadas.

Si bien el sujeto de la administración del compuesto de la presente invención no está particularmente limitado, se prefiere un mamífero (por ejemplo, ratón, rata, hámster, conejo, gato, perro, bovino, oveja, mono, humano y similares).

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Si bien la dosis del compuesto de la presente invención varía según el sujeto de administración, la vía de administración, la enfermedad blanco, los síntomas y similares, por ejemplo, para la administración oral a un paciente diabético adulto, generalmente es de aproximadamente 0,01 a 100 mg/kg de peso corporal, con preferencia 0,05 a 30 mg/kg de peso corporal, con mayor preferencia 0,1 a 10 mg/kg de peso corporal para una dosis, la cual se prefiere administrar de una a 3 veces por día.

Con el objeto de mejorar la acción del compuesto de la presente invención o disminuir la dosis del compuesto y similares, el compuesto se puede usar en combinación con medicamentos tales como agentes terapéuticos para diabetes, agentes terapéuticos para complicaciones diabéticas, agentes terapéuticos para hiperlipidemia, agentes antihipertensivos, agentes antiobesidad, diuréticos, agentes antitrombóticos y similares (en adelante abreviados como fármaco concomitante). El momento de la administración del compuesto de la presente invención y el del fármaco concomitante no están limitados y se pueden administrar en forma simultánea o gradual al sujeto de la administración. Además, el compuesto de la presente invención y el fármaco concomitante se pueden administrar como dos clases de preparaciones que contienen los respectivos ingredientes activos o como una única preparación que contiene ambos ingredientes activos.

La dosis del fármaco concomitando puede ser determinada en forma apropiada sobre la base de la dosis empleada clínicamente. Además, la proporción de la mezcla del

compuesto de la presente invención y el fármaco concomitante se pueden determinar apropiadamente de acuerdo con el sujeto de la administración, la vía de administración, la enfermedad blanco, la condición patológica, la combinación y similares. Por ejemplo, cuando el sujeto de la administración es un humano, el fármaco concomitante se puede usar en una cantidad de 0,01 a 100 partes en peso por 1 parte en peso del compuesto de la presente invención.

Los ejemplos de agente terapéutico para diabetes incluyen preparaciones de insulina [por ejemplo, preparaciones de insulina animal extraída de páncreas bovino o porcino; preparaciones de insulina human sintetizados mediante técnicas de ingeniería genética que utilizan *Escherichia coli* o una levadura; insulina zinc; insulina protamina zinc; un fragmento o un derivado de insulina (por ejemplo, INS-1, etc.)], preparación oral de insulina), sensibilizador de insulina (por ejemplo, pioglitazona o una de sus sales correspondientes (con preferencia clorhidrato), TAK-379, rosiglitazona o una de sus sales correspondientes (con preferencia maleato), tesaglitazar, ragaglitazar, muraglitazar, edaglitazona, metaglidaseno, Naveglitazar, AMG-131, THR-0921), inhibidor de α-glucosidasa (por ejemplo, voglibosa, acarbosa, miglitol, emiglitato), biguanida (por ejemplo, metformina, buformina o una de sus sales correspondientes (por ejemplo, clorhidrato, fumarato, succinato)), secretagogo de insulina [sulfonilurea (por ejemplo, tolbutamida, glibenclamida, gliclazida, clorpropamida, tolazamida, acetohexamida, gliclopiramida,

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glimepirida, glipizida, glibuzol), repaglinida, nateglinida, mitiglinida o una sal de hidrato de calcio correspondiente, secretagogo de insulina dependiente de glucosa (por ejemplo, TAK-875)], inhibidor de dipeptidilpeptidasa IV (por ejemplo, alogliptina, vildagliptina, sitagliptina, saxagliptina, T-6666, TS-021), β3-agonista (por ejemplo, AJ-9677), GPR40-agonista, agonista de receptor GLP-1 [por ejemplo, GLP-1, GLP-1MR, NN-2211, AC-2993 (exendina-4), BIM-51077, Aib(8,35)hGLP-1(7,37)$NH_2$, CJC-1131], agonista de amilina (por ejemplo, pramlintida), inhibidores de fosfotirosina fosfatasa (por ejemplo, vanadiato de sodio), inhibidor de gluconeogénesis (por ejemplo, inhibidor de glucógeno fosforilasa, inhibidores de glucosa-6-fosfatasa, antagonistas de glucagón), inhibidor de SGLUT (cotransprotador de sodio-glucosa) (por ejemplo, T-1095), inhibidor de 11β-hidroxisteroidedeshidrogenasa (por ejemplo, BVT-3498), adiponectina o uno de sus agonistas, inhibidor de IKK (por ejemplo, AS-2868), fármacos mejoradores de resistencia a leptina, agonistas de receptor de somatostatina, activadores de glucocinasa (por ejemplo, Ro-28-1675), GIP (péptido insulinotrópico dependiente de glucosa) y similares.

Los ejemplos de los agentes terapéuticos para las complicaciones diabéticas incluyen inhibidores de aldosarreductasa (por ejemplo, tolrestat, epalrestat, zenarestat, zopolrestat, minalrestat, fidarestat, CT-112), factor neurotrófico y uno de sus fármaco incrementadotes (por ejemplo, NGF, NT-3, BDNF, promotor de la producción y secreción de neurotrofina descrito en el documento WO01/14372

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(por ejemplo, 4-(4-clorofenil)-2-(2-metil-1-imidazolil)-5-[3-(2-metilfenoxi)propil]oxazol)), TAK-583, promotor de la regeneración nerviosa (por ejemplo, Y-128), inhibidor de PKC (por ejemplo, ruboxistaurinmesilato), inhibidor de AGE (por ejemplo, ALT946, pimagedina, piratoxantina, bromuro de N-fenaciltiazolio (ALT766), ALT-711, EXO-226, piridorina, piridoxamina), eliminadores de oxígeno activo (por ejemplo, ácido tióctico), vasodilatador cerebral (por ejemplo, tiapurida, mexiletina), agonistas de receptor de somatostatina (por ejemplo, BIM23190), inhibidor de cinasa 1 reguladora de la señal de apoptosis (ASK-1) y similares.

Los ejemplos de agente terapéutico para la hiperlipidemia incluyen compuestos de estatinas (por ejemplo, pravastatina, simvastatina, lovastatina, atorvastatina, fluvastatina, rosuvastatina, pitavastatina o una de sus sales correspondientes (por ejemplo, sal de sodio, sal de calcio)), inhibidores de escualenosintasa (por ejemplo, acetato de lapaquistat o una de sus sales correspondientes), compuesto de fibrato (por ejemplo, bezafibrato, clofibrato, simfibrato, clinofibrato), inhibidor de ACAT (por ejemplo, Avasimibe, Eflucimibe), resina de intercambio aniónico (por ejemplo, colestiramina), probucol, fármaco de ácido nicotínico (por ejemplo, nicomol, niceritrol), icosapentato de etilo, fitosterol (por ejemplo, soisterol, gamma orizanol (γ-orizanol)) y similares.

Los ejemplos de agente antihipertensivo incluyen inhibidores de enzima convertidora de angiotensina (por ejemplo, captoprilo, enalaprilo, delaprilo), antagonistas de

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angiotensina II (por ejemplo, candesartancilexetilo, losartan, eprosartan, valsartan, telmisartan, irbesartan, tasosartan, ácido 1-[[2'-(2,5-dihidro-5-oxo-4H-1,2,4-oxadiazol-3-il)bifenil-4-il]metil]-2-etoxi-1H-benzimidazol-7-carboxílico, TAK-491), antagonistas de calcio (por ejemplo, manidipina, nifedipina, amlodipina, efonidipina, nicardipina), abridor de canal de potasio (por ejemplo, levcromacalim, L-27152, AL 0671, NIP-121), clonidina y similares.

Los ejemplos de agente antiobesidad incluyen agentes antiobesidad de acción central (por ejemplo, dexfenfluramina, fenfluramina, fentermina, sibutramina, amfepramona, dexamfetamina, mazindol, fenilpropanolamina, clobenzorex; antagonistas de receptor de MCH (por ejemplo, SB-568849; SNAP-7941; compuestos descritos en los documentos WO01/82925 y WO01/87834); antagonista de neuropéptido Y (por ejemplo, CP-422935); antagonistas de receptor de cannabinoides (por ejemplo, SR-141716, SR-147778); antagonista de ghrelina; inhibidor de 11β-hidroxiesteroidedeshidrogenasa (por ejemplo, BVT-3498)), inhibidores de lipasa pancreática (por ejemplo, orlistat, cetilistat), β3 agonista (por ejemplo, AJ-9677, AZ40140), péptidos anorécticos (por ejemplo, leptina, CNTF (factor neurotrófico ciliar)), agonista de colecistocinina (por ejemplo, lintitript, FPL-15849), limitador del apetito (por ejemplo, P-57) y similares.

Los ejemplos de diuréticos incluyen derivados de xantina (por ejemplo, salicilato de teobromina sodio, salicilato de teobromina calcio), preparaciones de tiazidas (por ejemplo,

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etiazida, ciclopentiazida, triclorometiazida, hidroclorotiazida, hidroflumetiazida, bencilhidroclorotiazida, penflutizida, politiazida, meticlotiazida), preparaciones antialdosterona (por ejemplo, espironolactona, triamtereno), inhibidores de anhidrasa carbónica (por ejemplo, acetazolamida), agentes de clorobencenosulfonamida (por ejemplo, clortalidona, mefrusida, indapamida), azosemida, isosorbide, ácido etacrínico, piretanida, bumetanida y furosemida y similares.

Los ejemplos de agente antitrombótico incluyen heparina (por ejemplo, heparina de sodio, heparina de calcio, dalteparina de sodio (dalteparina de sodio)), warfarina (por ejemplo, warfarina de potasio), fármaco antitrombina (por ejemplo, aragatroban, dabigatran), agente trombolítico (por ejemplo, uroquinasa, tisoquinasa, alteplasa, nateplasa, monteplasa, pamiteplasa), inhibición de la agregación plaquetaria (por ejemplo, clorhidrato de ticlopidina, cilostazol), icosapentato de etilo, beraprost sodio, clorhidrato de sarpogrelato, E5555, SHC 530348, prasugrel), inhibidor de FXa (por ejemplo, TAK-442, rivaroxaban, apixaban, DU-176b, YM150) y similares.

Los fármacos concomitantes antes mencionados pueden ser una combinación de dos o más tipos en una relación apropiada.

Los métodos de producción del compuesto de la presente invención se explican a continuación.

El compuesto de la presente invención se puede producir de acuerdo con un método conocido per se, por ejemplo, los

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métodos descritos en detalle a continuación o un método análogo a ellos.

En los siguientes métodos de producción, los compuestos de material de inicio pueden estar en la forma de sales y los ejemplos de dichas sales incluyen los similares a las sales del compuesto (I) y el compuesto (IA).

El compuesto obtenido en cada etapa de las siguientes fórmulas se puede usar para la siguiente reacción directamente en la forma de la mezcla de reacción o un producto crudo o se puede aislar y purificar por medios conocidos de separación y purificación, por ejemplo, concentración, concentración a presión reducida, extracción por solventes, cristalización, recristalización, transferencia de fase, cromatografía y similares y usar para la siguiente reacción.

Cuando los compuestos de las siguientes fórmulas están disponibles en el comercio, se pueden usar directamente dichos productos disponibles en el comercio.

En cada una de las siguientes reacciones, cuando el compuesto de material de inicio tiene un grupo amino, un grupo carboxi o un grupo hidroxi como sustituyente, sicho grupo puede ser protegido mediante un grupo protector de uso general en la química de los péptidos y similares. En este caso, el grupo protector se retira según necesidad después de la reacción para dar el compuesto objetivo.

Los ejemplos de grupo protector de amino incluyen un grupo formilo, un alquil $C_{1-6}$-carbonilo, un grupo alcoxi $C_{1-6}$ carbonilo, un grupo benzoilo, un grupo aralquil $C_{7-10}$-

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carbonilo (por ejemplo, bencilcarbonilo), un grupo aralquiloxi $C_{7-14}$-carbonilo (por ejemplo, benciloxicarbonilo, 9-fluorenilmetoxicarbonilo), un grupo tritilo, un grupo ftaloilo, un grupo N,N-dimetilaminometileno, un grupo sililo sustituido (por ejemplo, trimetilsililo, trietilsililo, dimetilfenilsililo, ter-butildimetilsililo, ter-butildietilsililo), un grupo alquenilo $C_{2-6}$ (por ejemplo, 1-alilo) y similares. Estos grupos están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de un átomo de halógeno, un grupo alcoxi $C_{1-6}$ y un grupo nitro.

Los ejemplos de grupo protector de carboxi incluyen un grupo alquilo $C_{1-6}$, un grupo aralquilo $C_{7-11}$ (por ejemplo, bencilo), un grupo fenilo, un grupo tritilo, un grupo sililo sustituido (por ejemplo, trimetilsililo, trietilsililo, dimetilfenilsililo, ter-butildimetilsililo, ter-butildietilsililo), un grupo alquenilo $C_{2-6}$ (por ejemplo, 1-alilo) y similares.

Los ejemplos de grupo protector de hidroxi incluyen un grupo alquilo $C_{1-6}$, un grupo fenilo, un grupo tritilo, un grupo aralquilo $C_{7-10}$ (por ejemplo, bencilo), un grupo formilo, un grupo alquil $C_{1-6}$-carbonilo, un grupo benzoilo, un grupo aralquil $C_{7-10}$ -carbonilo (por ejemplo, bencilcarbonilo), un grupo 2-tetrahidropiranilo, un grupo 2-tetrahidrofuranoilo, un grupo sililo sustituido (por ejemplo, trimetilsililo, trietilsililo, dimetilfenilsililo, ter-butildimetilsililo, ter-butildietilsililo), un grupo alquenilo $C_{2-6}$ (por ejemplo, 1-alilo) y similares. Estos grupos están opcionalmente sustituidos con 1 a 3

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sustituyentes seleccionados de un átomo de halógeno, un grupo alquilo $C_{1-6}$, un grupo alcoxi $C_{1-6}$ y un grupo nitro.

Los grupos protectores antes mencionados se pueden eliminar de acuerdo con un método conocido per se, por ejemplo, el método descrito en Protective Groups in Organic Synthesis, John Wiley and Sons (1980) y similares. Específicamente, se usa un método que utiliza un ácido, una base, rayos ultravioletas, hidrazina, fenilhidrazina, N-metilditiocarbamato de sodio, fluoruro de tetrabutilamonio, acetato de paladio, haluro de trialquilsililo (por ejemplo, yoduro de trimetilsililo, bromuro de trimetilsililo y similares) y similares, un método de reducción y similares.

En cada una de las siguientes reacciones, la introducción del sustituyente y la conversión del grupo funcional también se pueden llevar a cabo mediante la aplicación de un método conocido per se al material de inicio, intermediario y/o producto resultante.

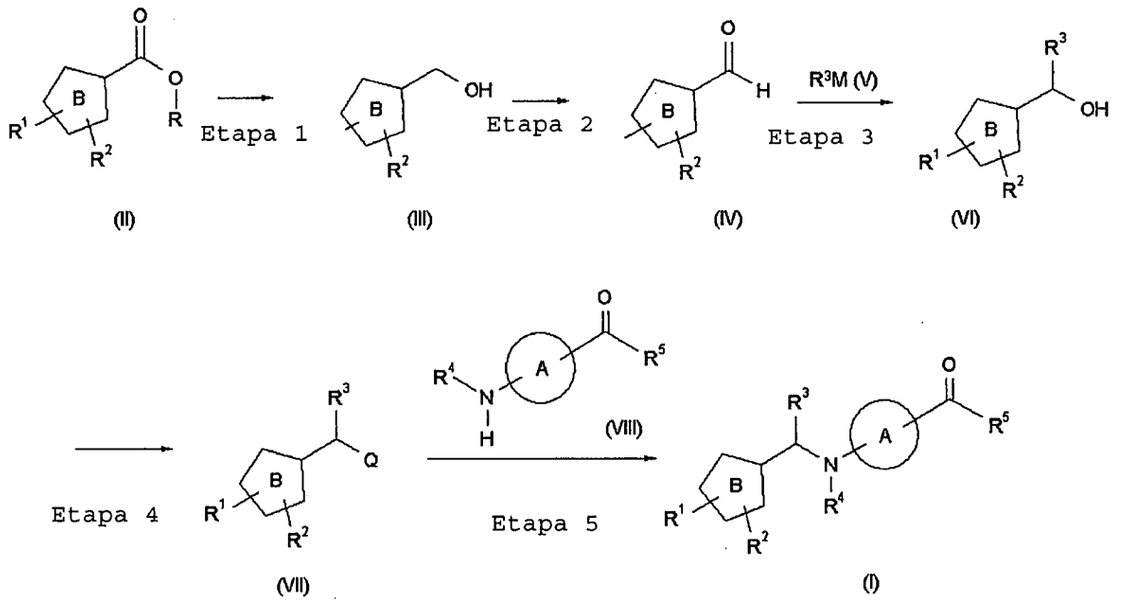
Los ejemplos de reacción de conversión de sustituyente incluyen métodos conocido per se, por ejemplo, la conversión a carboxi por hidrólisis de éster, la conversión a carbamoilo por amidación de carboxi, la conversión a hidroximetilo por reducción de carboxi, la conversión a compuesto alcohol por reducción o alquilación de carbonilo, aminación reductora de carbonilo, oximación de carbonilo, acilación, ureación, sulfonilación o alquilación de amino, sustitución y aminación de halógeno activo por amina, aminación de nitro por reducción, alquilación de hidroxi, sustitución y aminación de hidroxi; alquilación de átomo de nitrógeno del anillo de

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heterociclo que contiene nitrógeno, introducción de sustituyentes por reacción de acoplamiento (por ejemplo, reacción de acoplamiento de arilo); sustitución de halógeno por amina, alcohol o tiol; y similares.

El compuesto (I) puede ser producido, por ejemplo, mediante un método presentado en el siguiente Esquema de Reacción 1.

Esquema de reacción 1




en donde R es un grupo alquilo $C_{1-6}$ (por ejemplo, metilo, etilo, n-hexilo); Q es un grupo saliente (por ejemplo, grupo metansulfoniloxi, grupo p-toluensulfoniloxi, átomo de halógeno (por ejemplo, cloro, bromo)); $R^3M$ es compuesto de metal orgánico (mencionado posteriormente) y otros símbolos como se definieron anteriormente.

Etapa 1

El compuesto (III) se puede producir al someter al compuesto del material de partida (II) a una reacción de reducción. Esta reacción de reducción se puede realizar

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usando un agente reductor y de acuerdo con un método convencional.

Los ejemplos del agente reductor incluyen compuestos de hidrógeno metálico tal como hidruro de bis(2-metoxietoxi)aluminio y sodio, hidruro de diisobutilaluminio (DIBALH) y similares; compuestos de complejo de hidrógeno metálico tal como borohidruro de sodio, cianoborohidruro de sodio, hidruro de litio y aluminio, hidruro de aluminio y sodio y demás y similares.

La cantidad del agente reductor que se usa es, en general, 1 - 20 moles por 1 mol de compuesto (II).

Esta reacción se realiza con preferencia en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, se pueden mencionar alcoholes tales como metanol, etanol, propanol, isopropanol, butanol, isobutanol, ter-butanol y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, tricloroetileno y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, dimetoxietano y similares; ácidos minerales tales como ácido clorhídrico, ácido sulfúrico y similares; ácidos orgánicos tales como ácido fórmico, ácido acético, ácido propiónico, ácido trifluoroacético, ácido metansulfónico y similares; agua; y

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similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

El tiempo de reacción es, en general, 10 min - 48 h, con preferencia 15 min - 24 h.

La temperatura de reacción es, en general, -100 °C a 150 °C, con preferencia -20 °C a 100 °C.

El compuesto (II) que se usa como material de partida se puede sintetizar de acuerdo con un método conocido per se, por ejemplo, el método de síntesis descrito en los documentos WO 2007/89031, EP94154, WO2003/99793 o EP1176140 o un método análogo a este.

Etapa 2

El compuesto (IV) se puede producir al someter el compuesto (III) a una reacción de oxidación. La reacción de oxidación se puede realizar usando un oxidante y de acuerdo con un método convencional.

Los ejemplos del oxidante incluyen dióxido de manganeso activo, clorocromato de piridinio (PCC), dicromato de piridinio (PDC), peryodinano de Dess-Martin, dimetilsulfóxido-anhídrido ácido (por ejemplo, anhídrido acético, anhídrido trifluoroacético), dimetilsulfóxido-cloruro de tionilo, dimetilsulfóxido-cloruro de sulfurilo, dimetilsulfóxido-cloruro de oxalilo, dimetilsulfóxido-cloro y dimetilsulfóxido-diciclohexilcarbodiimida (DCC) en presencia de ácido (por ejemplo, ácido fosfórico, ácido trifluoroacético, ácido dicloroacético) y similares.

La cantidad del oxidante usado es, en general, 1 - 20 moles por 1 mol de compuesto (III).

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Esta reacción se realiza con preferencia en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, éteres tales como éter dietílico, éter diisopropílico, éter difenílico, tetrahidrofurano, 1,4-dioxano, 1,2-dimetoxietano y similares; cetonas tales como acetona, metiletilcetona y similares; hidrocarburos halogenados tal como diclorometano, cloroformo, tetracloruro de carbono, tricloroetileno y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; hidrocarburos saturados tales como ciclohexano, hexano y similares; amidas tal como N,N-dimetilformamida, N,N-dimetilacetamida, hexametilfosforamida y similares; ácidos minerales tal como ácido clorhídrico, ácido sulfúrico y similares; ácidos orgánicos tales como ácido fórmico, ácido acético, ácido propiónico, ácido trifluoroacético, ácido metansulfónico y similares; agua; y similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

El tiempo de reacción es, en general, 10 min - 48 h, con preferencia 15 min - 24 h.

La temperatura de reacción es, en general, -100 °C a 150 °C, con preferencia -20 °C a 100 °C.

Etapa 3

El compuesto (VI) se puede producir por la reacción del compuesto (IV) con el compuesto metálico orgánico (V).

Esta reacción se realiza en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado

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siempre que la reacción proceda y, por ejemplo, éteres tales como éter dietílico, tetrahidrofurano, 1,4-dioxano y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

Los ejemplos del compuesto metálico orgánico (V) incluyen reactivo de Grignard (por ejemplo, un compuesto representado por la fórmula: $R^3MgBr$), reactivo orgánico de litio (por ejemplo, un compuesto representado por la fórmula: $R^3Li$), reactivo orgánico de zinc (por ejemplo, a compuesto representado por la fórmula: $(R^3)_2Zn$), en donde $R^3$ es como se definió anteriormente) y similares. Dicho compuesto se puede producir de acuerdo con un método conocido per se, por ejemplo, el método descrito en "Jikken Kagaku Kouza (The Chemical Society of Japan ed.), 4a Edición, vol. 25, Synthesis by Organic Metal Reagent" pp. 9-449, Maruzen Press 1992 o un método análogo a este.

La cantidad del compuesto metálico orgánico (V) que se usa es, en general, aproximadamente 1 - 10 moles, con preferencia aproximadamente 1 - 2 moles, por 1 mol de compuesto (IV).

La temperatura de reacción es, en general, -80 °C a 100 °C, con preferencia -20 °C a 50 °C.

El tiempo de reacción es, en general, 0,5 - 20 h.

Etapa 4

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El compuesto (VII) se puede producir por la conversión del grupo hidroxi del compuesto (VI) a un grupo saliente.

Dicha conversión a un grupo saliente se puede realizar de acuerdo con un método convencional, por ejemplo, por la reacción con cloruro de metansulfonilo en presencia de una base apropiada o por la reacción con cloruro de tionilo.

Los ejemplos de base usada en esta reacción incluyen N,N-diisopropiletilamina (DIEA), trietilamina (TEA), piridina, N,N-dimetilanilina y similares.

La cantidad del cloruro de metansulfonilo o cloruro de tionilo que se usa es, en general, aproximadamente 1 - 50 moles, con preferencia aproximadamente 1 - 10 moles, por 1 mol de compuesto (VI).

La cantidad de base que se usa es, en general, aproximadamente 1 - 50 moles, con preferencia aproximadamente 1 - 10 moles, por 1 mol de compuesto (VI).

Esta reacción se realiza en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, se pueden usar éteres tales como éter dietílico, tetrahidrofurano, 1,4-dioxano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, -50 - 150 °C, con preferencia -10 - 100 °C.

El tiempo de reacción es, en general, 0,5 - 20 h.

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Etapa 5

El compuesto (I) se puede producir por la reacción del compuesto (VII) con el compuesto (VIII) (por ejemplo, 3-{((4-aminofenil)carbonil)amino}propanoato de etilo) en presencia de una base. Cuando sea necesario, el grupo éster del aducto obtenido se puede hidrolizar.

Los ejemplos de la base usada para esta reacción incluyen hidróxidos de metal alcalino tales como hidróxido de litio, hidróxido de sodio, hidróxido de potasio y similares; hidróxidos de metal alcalinotérreo tales como hidróxido de magnesio, hidróxido de calcio y similares; carbonatos de metal alcalino tales como carbonato de sodio, carbonato de potasio, carbonato de cesio y similares; carbonatos ácidos de metal alcalino tales como carbonato ácido de sodio, carbonato ácido de potasio y similares; alcóxidos de metal alcalino que tienen 1 a 6 átomos de carbono tales como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares; hidruros metálicos tal como hidruro de sodio, hidruro de potasio, hidruro de calcio y demás y similares.

Esta reacción se realiza con preferencia en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, alcoholes tal como metanol, etanol, 1-propanol, 2-propanol, alcohol ter-butílico y similares; éteres tales como 1,4-dioxano, tetrahidrofurano, éter dietílico, dimetoxietano, éter ter-butilmetílico, éter diisopropílico, dimetiléter de etilenglicol y similares; ésteres tales como formiato de etilo, acetato de etilo, acetato de n-butilo y similares;

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hidrocarburos halogenados tal como diclorometano, cloroformo, tetracloruro de carbono, tricloroetileno y similares; hidrocarburos tal como n-hexano, benceno, tolueno y similares; amidas tales como formamida, N,N-dimetilformamida, N,N-dimetilacetamida y similares; nitrilos tales como acetonitrilo, propionitrilo y similares; sulfóxidos tales como dimetilsulfóxido y similares; sulfolano; hexametilfosforamida; y similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

En esta reacción, se puede agregar 1 cantidad equivalente a una cantidad de exceso grande (con preferencia 1 - 10 equivalentes) de yoduro de metal alcalino tal como yoduro de sodio y similares como un promotor de reacción al compuesto (VII).

La cantidad del compuesto (VIII) que se usa es, en general, aproximadamente 1 - 10 moles, con preferencia aproximadamente 1 - 2 moles, por 1 mol de compuesto (VII).

La cantidad de base que se usa es, en general, 1 - 10 equivalentes molares, con preferencia 1 - 5 equivalentes molares, por 1 mol de compuesto (VII).

La temperatura de reacción es, en general, -30 - 200 °C, con preferencia 0 - 150 °C.

El tiempo de reacción es, en general, 0,5 - 20 h.

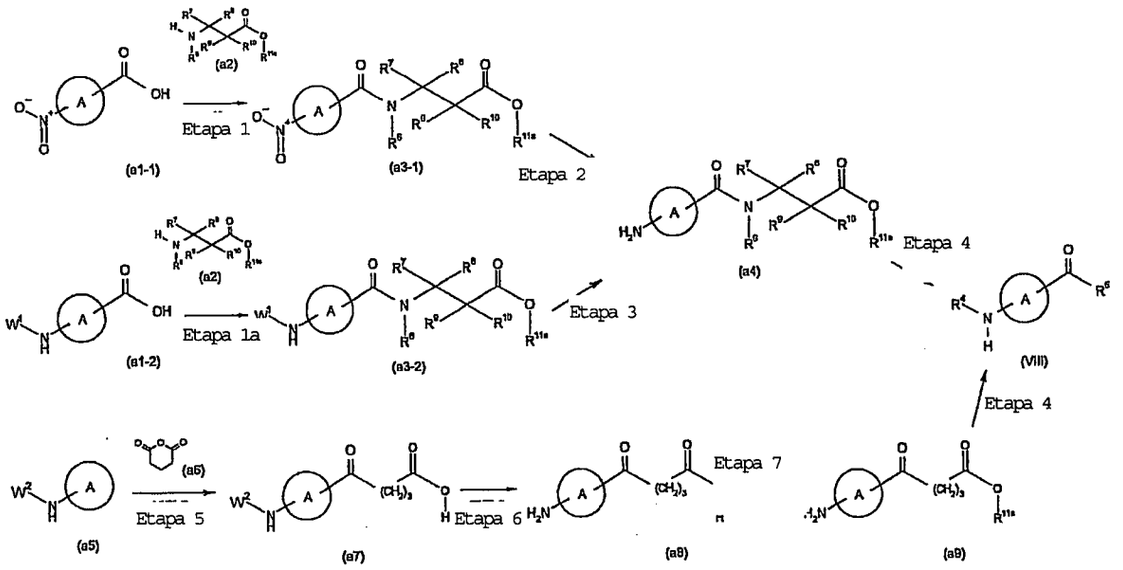
El grupo éster se puede hidrolizar de acuerdo con un método conocido per se, por ejemplo, el método descrito en Protective Groups in Organic Synthesis, Tercera edición, Wiley-Interscience (1999) o un método análogo a este.

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Los métodos de producción del compuesto material de partidas y sus derivados reactivos usados para los métodos mencionados anteriormente se explican a continuación.

El compuesto (VIII) se puede producir de acuerdo con, por ejemplo, el siguiente esquema de reacción 2.

Esquema de reacción 2




en donde $W^1$ y $W^2$ son de modo independiente un grupo protector de amino, $R^{11a}$ es un grupo alquilo $C_{1-6}$ y otros símbolos como se definieron anteriormente.

Etapa 1

En esta reacción, el compuesto (a1-1) se condensa con el compuesto (a2) para dar el compuesto (a3-1).

La reacción de condensación se puede realizar de acuerdo con un método convencional, por ejemplo, un método de acoplamiento de péptidos general. Los ejemplos del método incluyen un método que incluye condensación directa del compuesto (a1-1) y el compuesto (a2) usando un agente de condensación, un método que incluye la reacción de un

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derivado reactivo del compuesto (a1-1) con el compuesto (a2) y similares.

Los ejemplos del agente de condensación incluyen los reactivos de condensación de carbodiimida tales como diciclohexilcarbodiimida (DCC), diisopropilcarbodiimida (DIPC), 1-etil-3-(3-dimetilaminopropil)carbodiimida (EDC), sus clorhidratos y similares; reactivos de condensación con ácido fosfórico tales como cianofosfato de dietilo, difenilfosforilazida y similares; carbonildiimidazol, tetrafluoroborato de 2-cloro-1,3-dimetilimidazolio, hexafluorofosfato de 2-(7-aza-1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio (HATU) y similares.

Los ejemplos del solvente usado para la reacción de condensación incluyen amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como dimetilsulfóxido y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico, dimetoxietano y similares; ésteres tales como acetato de metilo, acetato de etilo y similares; nitrilos tales como acetonitrilo, propionitrilo y similares; agua; y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del compuesto (a2) que se usa es, en general, 1 - 10 moles, con preferencia 1 - 3 moles, por 1 mol de compuesto (a1-1).

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La cantidad del agente de condensación que se usa es, en general, 0,1 - 10 moles, con preferencia 0,3 - 3 moles, por 1 mol de compuesto (a1-1).

Cuando se usa un reactivo de condensación de carbodiimida como el agente de condensación, se puede mejorar la eficiencia de reacción usando un promotor de condensación adecuado (por ejemplo, 1-hidroxi-7-azabenzotriazol, 1-hidroxibenzotriazol, N-hidroxisuccinimida, N-hidroxiftalimida) según corresponda.

Cuando se usa HATU o un reactivo de condensación de ácido fosfórico como el agente de condensación, se puede mejorar la eficiencia de reacción usando una base de orgánica tal como trietilamina, N,N-diisopropiletilamina y similares.

La cantidad del promotor de condensación o base de amina orgánica que se usa es, en general, 0,1 - 10 moles, con preferencia 0,3 - 3 moles, por 1 mol de compuesto (a1-1), respectivamente.

La temperatura de reacción es, en general, -30 - 120 °C, con preferencia -10 - 100 °C.

El tiempo de reacción es, en general, 0,5 - 60 h.

Los ejemplos del derivado reactivo del compuesto (a1-1) incluyen haluro ácido (por ejemplo, cloruro ácido, bromuro ácido), imidazolida, anhídrido ácido mixto (por ejemplo, anhídrido con carbonato de metilo, carbonato de etilo o carbonato de isobutilo) y similares.

Por ejemplo, cuando se usa un haluro ácido, la reacción se realiza generalmente en presencia de una base y en un solvente que no influencia adversamente la reacción.

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Los ejemplos de la base incluyen aminas tales como trietilamina, piridina, N-metilmorfolina, N,N-dimetilanilina, 4-dimetilaminopiridina y similares; sal de metal alcalino tal como hidróxido de litio, hidróxido de sodio, hidróxido de potasio, carbonato ácido de sodio, carbonato de sodio, carbonato de potasio y similares; y similares.

Los ejemplos del solvente que se pueden mencionar que no influencian adversamente la reacción incluyen amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como dimetilsulfóxido y similares; hidrocarburos halogenados tal como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico, dimetoxietano y similares; ésteres tales como acetato de metilo, acetato de etilo y similares; nitrilos tales como acetonitrilo, propionitrilo y similares; agua; y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

Cuando la amida anteriormente mencionada se usa como solvente, la reacción también se puede realizar en ausencia de una base.

La cantidad del compuesto (a2) que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de haluro ácido de compuesto (a1-1).

La cantidad de base que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de haluro ácido de compuesto (a1-1).

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La temperatura de reacción es, en general, -30 °C - 120 °C, con preferencia -10 - 100 °C.

El tiempo de reacción es, en general, 0,5 - 30 h.

Cuando se usa un anhídrido ácido mixto, el compuesto (a1-1) se hace reaccionar con clorocarbonato (por ejemplo, clorocarbonato de metilo, clorocarbonato de etilo, clorocarbonato de isobutilo) en presencia de una base y luego se hace reaccionar con el compuesto (a2).

Los ejemplos de la base usada para esta reacción incluyen los anteriormente mencionados, los ejemplificados como base usada para la reacción de un haluro ácido del compuesto (a1-1) con el compuesto (a2) y similares.

La cantidad del compuesto (a2) que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (a1-1).

La cantidad del clorocarbonato que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (a1-1).

La cantidad de base que se usa es, en general, 1 - 10 moles, con preferencia 1 - 3 moles, por 1 mol de compuesto (a1-1).

La temperatura de reacción es, en general, -30 °C - 120 °C, con preferencia -10 - 100 °C.

El tiempo de reacción es, en general, 0,5 - 20 h.

Cuando se usa imidazolida, el compuesto (a1-1) se hace reaccionar con, por ejemplo, N,N'-carbonildiimidazol (CDI) para dar la imidazolida correspondiente, que se hace reaccionar adicionalmente con el compuesto (a2).

La cantidad del compuesto (a2) que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (a1-1).

La cantidad de N,N'-carbonildiimidazol (CDI) que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (a1-1).

La temperatura de reacción es, en general, -30 °C - 120 °C, con preferencia -10 - 100 °C.

El tiempo de reacción es, en general, 0,5 - 20 h.

Como compuesto (a1-1) y compuesto (a2), se dispone de productos disponibles en el comercio o se pueden producir usando un compuesto disponible en el comercio de acuerdo con un método conocido per se o un método análogo a este.

Etapa 1a

El compuesto (a3-2) de la misma manera que en la etapa 1 y usando el compuesto (a1-2) y el compuesto (a2).

Como compuesto (a1-2), se puede usar un producto disponible en el comercio o se puede producir usando un compuesto disponible en el comercio de acuerdo con un método conocido per se o un método análogo a este.

Etapa 2

El compuesto (a4) se puede producir al someter el compuesto (a3-1) a una reacción de reducción en presencia de un catalizador metálico y una fuente de hidrógeno. Dicha reacción de reducción se puede realizar de acuerdo con un método convencional en un solvente que no influencia adversamente la reacción.

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Los ejemplos del catalizador metálico usado para esta reacción incluyen paladio-carbono, negro de paladio, cloruro de paladio, óxido de platino, negro de platino, platino-paladio, Raney-níquel, cobalto Raney y similares.

Los ejemplos de la fuente de hidrógeno incluyen gas hidrógeno, ácido fórmico, sal ácido fórmico amina, sal fosfinato, hidrazina y similares.

Los ejemplos del solvente que no influencia adversamente la reacción incluyen metanol, tetrahidrofurano, N,N-dimetilacetamida y similares.

La cantidad del catalizador metálico que se usa es, en general, 0,001 - 1000 moles, con preferencia 0,01 - 100 moles, por 1 mol de compuesto (a3-1).

La temperatura de reacción es, en general, -70 - 150 °C, con preferencia -20 - 100 °C.

El tiempo de reacción es, en general, 0,1 - 100 h, con preferencia 0,1 - 40 h.

Esta reacción también se puede realizar en presencia de un agente reductor en un solvente que no influencia adversamente la reacción.

Los ejemplos del agente reductor incluyen óxido férrico, zinc, estaño y similares y el compuesto (a4) se puede producir por la reacción descripta en "Jikken Kagaku Kouza (The Chemical Society of Japan ed.), 4a edición, vol. 20, Organic Synthesis II Alcohol and Amine" pp. 279-280, Maruzen Press 1992 o un método análogo a este.

Etapa 3

El compuesto (a4) se puede producir por la eliminación del grupo protector ($W^1$) del compuesto (a3-2) por un método conocido per se, por ejemplo, el método descrito en Protective Groups in Organic Synthesis, Tercera edición, Wiley-Interscience (1999) o un método análogo a este.

Etapa 4

El compuesto (VIII) se puede producir al someter el compuesto (a4) o compuesto (a9) a una reacción de aminación reductora.

La reacción de aminación reductora se puede realizar por un método conocido per se, por ejemplo, el método descrito en "Jikken Kagaku Kouza (The Chemical Society of Japan ed.), 4t Edición, vol. 20. Organic Synthesis II Alcohol and Amine" pp. 300-302, Maruzen Press 1992; el método descrito en Reductions in Organic Chemistry Segunda edición, American Chemical Society (1996), pp. 187-189; o un método análogo a este.

Etapa 5

El compuesto (a7) se puede sintetizar por la reacción de Friedel-Crafts usando el compuesto (a5) y anhídrido glutárico (a6) y por el método de síntesis descrito en, por ejemplo, el documento WO 2004/45616 o un método análogo a este.

Etapa 6

El compuesto (a8) se puede producir por la eliminación del grupo protector de compuesto (a7) por un método conocido per se, por ejemplo, el método descrito en Protective Groups in Organic Synthesis, Tercera edición, Wiley-Interscience (1999) o un método análogo a este.

Etapa 7

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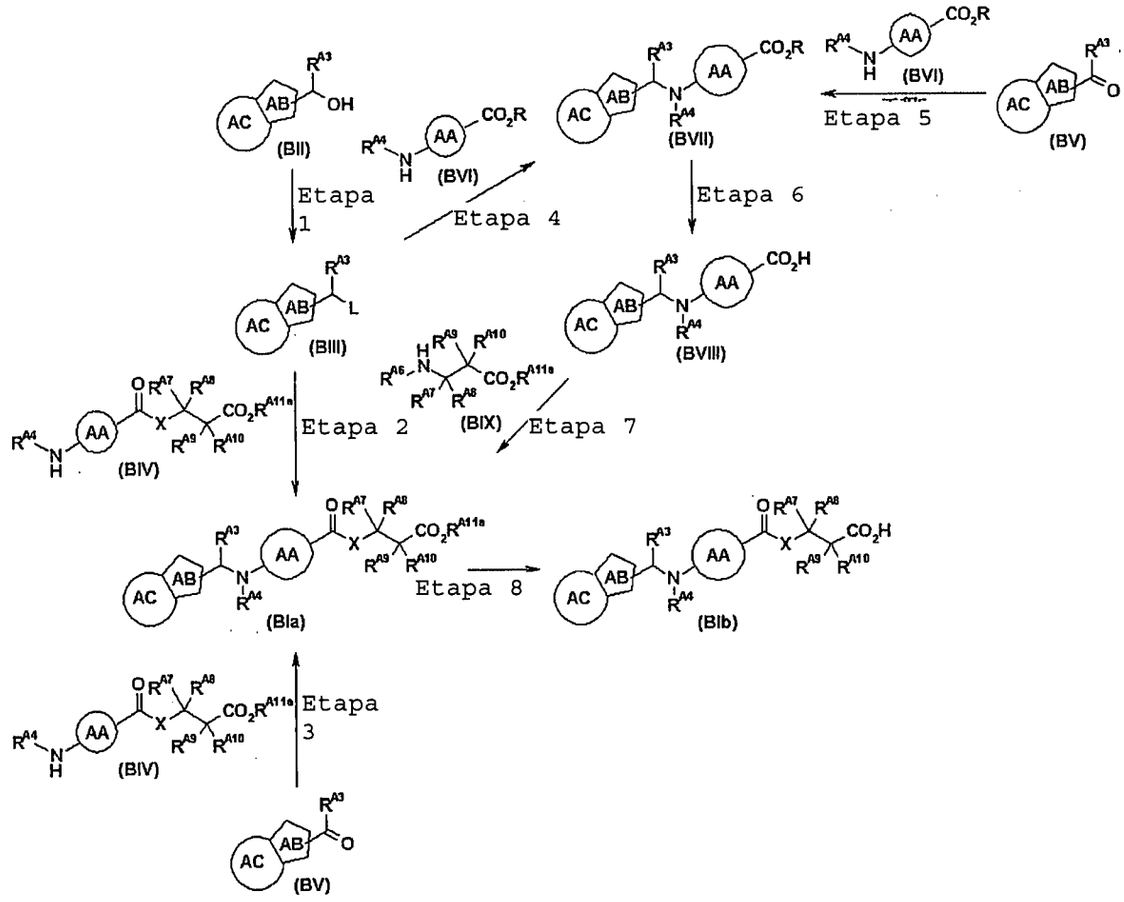
El compuesto (a9) se puede producir por esterificación del compuesto (a8) por un método conocido per se, por ejemplo, el método descrito en Protective Groups in Organic Synthesis, Tercera edición, Wiley-Interscience (1999) o un método análogo a este.

El compuesto (IA) se puede producir, por ejemplo, por el método mostrado en el siguiente esquema de reacción A1.

En el siguiente esquema de reacción A1, el compuesto (BIa) incluye un compuesto (IA) en donde $R^{A11}$ es el grupo alquilo $C_{1-6}$ y el compuesto (BIb) incluye un compuesto (IA) en donde $R^{A11}$ es un átomo de hidrógeno.

Esquema de reacción A1

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en donde X es $CH_2$ o $NR^{A6}$, $R^{A11a}$ es un grupo alquilo $C_{1-6}$, L es un grupo saliente (por ejemplo, grupo metansulfoniloxi, grupo p-toluensulfoniloxi, átomo de halógeno (por ejemplo, cloro, bromo)) y otros símbolos son como se definieron anteriormente.

Etapa 1

El compuesto (BIII) se puede producir, por ejemplo, por conversión del grupo hidroxi del compuesto (BII) a un grupo saliente. Dicha conversión a un grupo saliente se puede realizar de acuerdo con un método convencional, por ejemplo, reacción con cloruro de metansulfonilo, cloruro de fosforilo o cloruro de tionilo en presencia de una base apropiada.

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Los ejemplos de la base incluyen N,N-diisopropiletilamina (DIEA), trietilamina (TEA), piridina, N,N-dimetilanilina y similares.

La cantidad de base que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (BII).

La cantidad del cloruro de metansulfonilo, cloruro de fosforilo o cloruro de tionilo que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (BII).

Esta reacción se puede realizar en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, se pueden mencionar éteres tales como éter dietílico, tetrahidrofurano, 1,4-dioxano y similares; hidrocarburos halogenados tal como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, -80 - 200 °C, con preferencia -10 - 150 °C.

El tiempo de reacción es, en general, 10 min - 20 h, con preferencia 15 min - 24 h.

El compuesto (BII) se puede producir por la reacción mencionada a continuación.

Etapa 2

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El compuesto (BIa) se puede producir, por ejemplo, por la reacción del compuesto (BIII) con el compuesto (BIV) en presencia de una base.

Los ejemplos de base incluyen hidróxidos de metal alcalino tales como hidróxido de litio, hidróxido de sodio, hidróxido de potasio y similares; hidróxidos de metal alcalinotérreo tales como hidróxido de magnesio, hidróxido de calcio y similares; carbonatos de metal alcalino tales como carbonato de sodio, carbonato de potasio, carbonato de cesio y similares; carbonatos ácidos de metal alcalino tales como carbonato ácido de sodio, carbonato ácido de potasio y similares; alcóxidos de metal alcalino que tienen 1 a 6 átomos de carbono tal como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares; hidruros metálicos tal como hidruro de sodio, hidruro de potasio, hidruro de calcio y similares; y similares.

La cantidad de base que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (BIII).

Esta reacción se realiza con preferencia en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, se pueden mencionar alcoholes tales como metanol, etanol, 1-propanol, 2-propanol, alcohol ter-butílico y similares; éteres tales como 1,4-dioxano, tetrahidrofurano, éter dietílico, dimetoxietano, éter ter-butilmetílico, éter diisopropílico, dimetiléter de etilenglicol y similares; ésteres tales como formiato de etilo, acetato de etilo,

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acetato de isopropilo, acetato de n-butilo y similares; hidrocarburos halogenados tal como diclorometano, cloroformo, tetracloruro de carbono, tricloroetileno y similares; hidrocarburos tales como n-hexano, benceno, tolueno y similares; amidas tales como formamida, N,N-dimetilformamida, N,N-dimetilacetamida y similares; nitrilos tales como acetonitrilo, propionitrilo y similares; sulfóxidos tales como dimetilsulfóxido y similares; sulfolano; hexametilfosforamida; y similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

En esta reacción, se pueden añadir yoduro de metal alcalino tal como yoduro de sodio, yoduro de potasio y similares como promotor de la reacción, en a proporción de generalmente 1 - 20 moles, con preferencia 1 - 10 moles, por 1 mol de compuesto (BIII).

La cantidad del compuesto (BIV) que se usa es, en general, 1 - 10 moles, con preferencia 1 - 3 moles, por 1 mol de compuesto (BIII).

La temperatura de reacción es, en general, -80 °C - 200 °C, con preferencia 0 °C - 150 °C.

El tiempo de reacción es, en general, 10 min - 48 h, con preferencia 15 min - 24 h.

El compuesto (BIV) se puede producir por la reacción mencionada a continuación.

Etapa 3

El compuesto (BIa) se puede producir por un método conocido per se, por ejemplo, el método descrito en

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Reductions in Organic Chemistry Segunda Edición, American Chemical Society (1996), pp. 187-189; Journal of Chemical Society Perkin Transactions 1, (2000), pp. 145-146 y similares o un método análogo a este, al someter el compuesto (BV) y compuesto (BIV) a una reacción de aminación reductora.

El compuesto (BV) se puede producir por la reacción mencionada a continuación.

Etapa 4

El compuesto (BVII) se puede producir, por ejemplo, por la reacción del compuesto (BIII) con el compuesto (BVI) en presencia de una base de acuerdo con el método de producción del compuesto (BIa) a partir del compuesto (BIII).

Como compuesto (BVI), se puede usar un producto disponible en el comercio o se puede producir a partir de un compuesto disponible en el comercio por un método conocido per se o un método análogo a este.

Etapa 5

El compuesto (BVII) se puede producir al someter el compuesto (BV) y el compuesto (BVI) a una reacción de aminación reductora de acuerdo con el método de producción de, por ejemplo, el compuesto (BIa) a partir del compuesto (BV).

Etapa 6

El compuesto (BVIII) se puede producir por la hidrólisis del éster del compuesto (BVII) por un método conocido per se, por ejemplo, el método descrito en Protective Groups in Organic Synthesis, Tercera edición, Wiley-Interscience (1999) o un método análogo a este.

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Etapa 7

El compuesto (BIa) se puede producir por, por ejemplo, condensación del compuesto (BVIII) y el compuesto (BIX).

La reacción de condensación se puede realizar de acuerdo con un método convencional, por ejemplo, un método general de acoplamiento de péptidos. Los ejemplos de dicho método incluyen un método que incluye la condensación directa del compuesto (BVIII) y el compuesto (BIX) usando un agente de condensación o un método que incluye la reacción de un derivado reactivo del compuesto (BVIII) con el compuesto (BIX) y similares.

Los ejemplos del agente de condensación incluyen reactivos de condensación de carbodiimida tales como diciclohexilcarbodiimida (DCC), diisopropilcarbodiimida (DIPC), 1-etil-3-(3-dimetilaminopropil)carbodiimida (EDC) y sus clorhidratos y similares; reactivos de condensación con ácido fosfórico tal como cianofosfato de dietilo, difenilfosforilazida y similares; carbonildiimidazol, 2-tetrafluoroborato de cloro-1,3-dimetilimidazolio, O-(7-hexafluorofosfato de azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio (HATU) y similares.

Los ejemplos del solvente usado para la condensación directa usando un agente de condensación incluyen amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como dimetilsulfóxido y similares; hidrocarburos halogenados tal como cloroformo, diclorometano y similares; hidrocarburos alifáticos tales como hexano, heptano y similares;

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hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico, dimetoxietano, éter ter-butilmetílico y similares; ésteres tales como acetato de metilo, acetato de etilo, acetato de isopropilo, acetato de n-butilo y similares; nitrilos tales como acetonitrilo, propionitrilo y similares; agua; y similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

La cantidad del agente de condensación que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (BVIII).

Cuando se usa reactivo de condensación de carbodiimida como el agente de condensación, se puede mejorar la eficiencia de la reacción con el uso de un promotor de condensación adecuado (por ejemplo, 1-hidroxi-7-azabenzotriazol, 1-hidroxibenzotriazol, N-hidroxisuccinimida, N-hidroxiftalimida) según corresponda.

Cuando se usa HATU o reactivo de condensación con ácido fosfórico como el agente de condensación, se puede mejorar la eficiencia de la reacción con el uso de una base de amina orgánica tal como trietilamina, N,N-diisopropiletilamina y similares.

La cantidad del promotor de condensación o base de amina orgánica que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (BVIII), respectivamente.

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La cantidad del compuesto (BIX) que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (BVIII).

El tiempo de reacción es, en general, 10 min - 60 h, con preferencia 15 min - 24 h.

La temperatura de reacción es, en general, -50 - 150 °C, con preferencia -10 - 100 °C.

Los ejemplos del derivado reactivo del compuesto (BVIII) incluyen haluro ácido (por ejemplo, cloruro ácido, bromuro ácido), imidazolida, anhídrido ácido mixto (por ejemplo, anhídridos con carbonato de metilo, carbonato de etilo, carbonato de isobutilo y similares) y similares.

Cuando se usa un haluro ácido como derivado reactivo del compuesto (BVIII), la reacción se realiza generalmente en presencia de una base en un solvente inerte para la reacción.

Los ejemplos de base incluyen aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, 4-dimetilaminopiridina y similares; sales de metal alcalino tal como hidróxido de litio, hidróxido de sodio, hidróxido de potasio, carbonato ácido de sodio, carbonato de sodio, carbonato de potasio y similares; y similares.

La cantidad de base que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de haluro ácido de compuesto (BVIII).

Los ejemplos del solvente usado para esta reacción incluyen amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos

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tales como dimetilsulfóxido y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico, dimetoxietano, éter ter-butilmetílico y similares; ésteres tales como acetato de metilo, acetato de etilo, acetato de isopropilo, acetato de n-butilo y similares; nitrilos tales como acetonitrilo, propionitrilo y similares; agua; y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada. Cuando se usa la amida anteriormente mencionada como un solvente inerte para la reacción, la reacción también se puede realizar en ausencia de la base.

La cantidad del compuesto (BIX) que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de haluro ácido de compuesto (BVIII).

La temperatura de reacción es, en general, -30 °C - 150 °C, con preferencia -10 - 100 °C.

El tiempo de reacción es, en general, 10 min - 48 h, con preferencia 15 min - 24 h.

Cuando se usa anhídrido ácido mixto como derivado reactivo del compuesto (BVIII), el compuesto (BVIII) se hace reaccionar con clorocarbonato (por ejemplo, clorocarbonato de metilo, clorocarbonato de etilo, clorocarbonato de isobutilo) en presencia de una base y luego reacciona con el compuesto (BIX).

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Los ejemplos de la base usada para esta reacción incluyen los ejemplificados como la base usada para la reacción anteriormente mencionada de haluro ácido de compuesto (BVIII) con el compuesto (BIX).

La cantidad del clorocarbonato que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (BVIII).

La cantidad de base que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (BVIII).

La cantidad del compuesto (BIX) que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (BVIII).

La temperatura de reacción es, en general, -30 °C - 120 °C, con preferencia -10 - 100 °C.

El tiempo de reacción es, en general, 10 min - 48 h, con preferencia 15 min - 24 h.

Como el compuesto (BIX), se puede usar un producto disponible en el comercio o se puede producir a partir de un compuesto disponible en el comercio por un método conocido per se o un método análogo a este.

Etapa 8

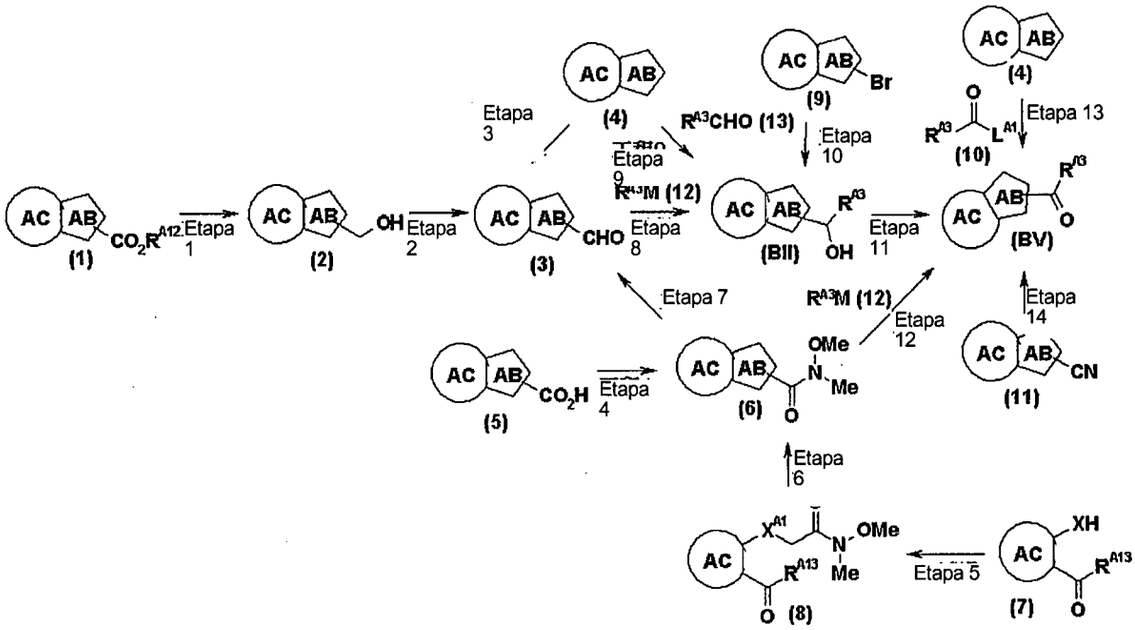
El compuesto (BIb) se puede producir, por ejemplo, por la hidrólisis del éster del compuesto (BIa) de acuerdo con el método de producción del compuesto (BVIII).

El Compuesto (BII) y compuesto (BV) los cuales son compuestos de material de inicio de Esquema de reacción A1 se

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puede producir, por ejemplo, por el método mostrado en el siguiente esquema de reacción A2.

Esquema de reacción A2




en donde $X^{A1}$ es $NR^{A14}$, O o S; $R^{A12}$ es un grupo alquilo $C_{1-6}$; $R^{A13}$ y $R^{A14}$ son de modo independiente un átomo de hidrógeno o un sustituyente que tiene opcionalmente el anteriormente mencionado anillo AB; $R^{A3}M$ es el compuesto de metal orgánico (mencionado posteriormente); $L^{A1}$ es un grupo saliente (por ejemplo, átomo de halógeno tal como cloro, bromo y similares) y otros símbolos como se definieron anteriormente.

Etapa 1

El compuesto (2) se puede producir al someter el compuesto (1) a una reacción de reducción. La reacción de reducción se puede realizar de acuerdo con un método convencional usando un agente reductor.

Los ejemplos del agente reductor incluyen compuestos de hidrógeno metálico tal como hidruro de bis(2-metoxietoxi)aluminio y sodio, hidruro de diisobutilaluminio

(DIBALH) y similares; compuestos de complejo de hidrógeno metálico tal como borohidruro de sodio, cianoborohidruro de sodio, hidruro de litio y aluminio, hidruro de aluminio y sodio, borohidruro de calcio y similares; y similares.

La cantidad del agente reductor que se usa es, en general, 1 - 20 moles, con preferencia 1 - 10 moles, por 1 mol de compuesto (1).

Esta reacción se realiza con preferencia en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, se pueden mencionar alcoholes tales como metanol, etanol, propanol, isopropanol, butanol, isobutanol, ter-butanol y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, tricloroetileno y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, dimetoxietano y similares; agua; y similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

El tiempo de reacción es, en general, 10 min - 48 h, con preferencia 15 min - 24 h.

La temperatura de reacción es, en general, -100 °C - 150 °C, con preferencia -20 °C - 100 °C.

Como compuesto (1), se puede usar un producto disponible en el comercio o se puede producir a partir de un compuesto

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disponible en el comercio por un método conocido per se o un método análogo a este.

Etapa 2

El compuesto (3) se puede producir, por ejemplo, por someter el compuesto (2) a una reacción de oxidación. La reacción de oxidación se puede realizar de acuerdo con un método convencional y usando un oxidante.

Los ejemplos del oxidante incluyen dióxido de manganeso activo, clorocromato de piridinio (PCC), dicromato de piridinio (PDC), peryodinano de Dess-Martin, dimetilsulfóxido-anhídrido ácido (por ejemplo, anhídrido acético, anhídrido trifluoroacético), dimetilsulfóxido-cloruro de tionilo, dimetilsulfóxido-cloruro de sulfurilo, dimetilsulfóxido-cloruro de oxalilo, dimetilsulfóxido-cloro y dimetilsulfóxido-diciclohexilcarbodiimida (DCC) en presencia de ácido (por ejemplo, ácido fosfórico, ácido trifluoroacético, ácido dicloroacético) y similares.

La cantidad del oxidante que se usa es, en general, 1 - 100 moles, con preferencia 1 - 50 moles, por 1 mol de compuesto (2).

Esta reacción se realiza con preferencia en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, se pueden mencionar éteres tales como éter dietílico, éter diisopropílico, éter difenílico, tetrahidrofurano, 1,4-dioxano, 1,2-dimetoxietano, ter-butilmetileter y similares; cetonas tales como acetona, metiletilcetona y similares; hidrocarburos halogenados tales

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como diclorometano, cloroformo, tetracloruro de carbono, tricloroetileno y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; hidrocarburos saturados tales como ciclohexano, hexano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, hexametilfosforamida y similares; nitrilos tales como acetonitrilo, propionitrilo y similares; ácidos minerales tal como ácido clorhídrico, ácido sulfúrico y similares; ácidos orgánicos tales como ácido fórmico, ácido acético, ácido propiónico, ácido trifluoroacético, ácido metansulfónico y similares, agua; y similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

El tiempo de reacción es, en general, 10 min - 48 h, con preferencia 15 min - 24 h.

La temperatura de reacción es, en general, -100 - 150 °C, con preferencia -20 - 100 °C.

Etapa 3

El compuesto (3) se puede producir, por ejemplo, por el tratamiento del compuesto (4) con una base y la reacción del compuesto con un agente de formilación.

Los ejemplos de la base usada para esta reacción incluyen, compuestos orgánicos de litio tales como n-butil-litio, sec-butil-litio, ter-butil-litio y similares y amidas alcalinas tales como diisopropilamida de litio, tris(trimetilsilil)amida de litio y similares.

La cantidad de base que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (4).

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Los ejemplos del agente de formilación incluyen N,N-dimetilformamida, N-formilpiperidina, ortoformiato de etilo y similares.

La cantidad del agente de formilación que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (4).

Esta reacción se realiza con preferencia en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, se pueden mencionar éteres tales como 1,4-dioxano, tetrahidrofurano, éter dietílico, éter ter-butilmetílico, éter diisopropílico, dimetiléter de etilenglicol y similares; hidrocarburos tales como n-hexano, n-pentano y similares; y similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

El tiempo de reacción es, en general, 10 min - 48 h, con preferencia 15 min - 24 h.

La temperatura de reacción es, en general, -100 - 100 °C, con preferencia -80 - 50 °C.

Como compuesto (4), se puede usar un producto disponible en el comercio o se puede producir a partir de un compuesto disponible en el comercio por un método conocido per se o un método análogo a este.

Etapa 4

El compuesto (6) se puede producir por condensación del compuesto (5) y N,O-dimetilhidroxilamina de acuerdo con el

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método de producción, por ejemplo, del compuesto (B1a) a partir del compuesto (BVIII).

Como compuesto (5), se puede usar un producto disponible en el comercio o se puede producir a partir de un compuesto disponible en el comercio por un método conocido per se o un método análogo a este.

Etapa 5

El compuesto (8) se puede producir por la reacción, por ejemplo, del compuesto (7) con 2-cloro-N-metoxi-N-metilacetamida en presencia de una base de acuerdo con el método de producción del compuesto (B1a) a partir del compuesto (BIII).

Como el compuesto (7), se puede usar un producto disponible en el comercio o se puede producir a partir de un compuesto disponible en el comercio por un método conocido per se o un método análogo a este.

Etapa 6

El compuesto (6) se puede producir, por ejemplo, por la reacción del compuesto (8) con una base.

Los ejemplos de la base incluyen hidróxidos de metal alcalino tales como hidróxido de litio, hidróxido de sodio, hidróxido de potasio y similares; hidróxidos de metal alcalinotérreo tales como hidróxido de magnesio, hidróxido de calcio y similares; carbonatos de metal alcalino tales como carbonato de sodio, carbonato de potasio, carbonato de cesio y similares; carbonatos ácidos de metal alcalino tales como carbonato ácido de sodio, carbonato ácido de potasio y similares; alcóxidos de metal alcalino que tienen 1 a 6

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átomos de carbono tal como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares; hidruros metálicos tal como hidruro de sodio, hidruro de potasio, hidruro de calcio y similares; bases orgánicas tal como 1,8-diazabiciclo[5,4,0]undec-7-eno (DBU), 1,5-diazabiciclo[4,3,0]non-5-eno (DBN), 1,4-diazabiciclo[2,2,2]octano (DABCO) y similares; y similares.

La cantidad de base que se usa es, en general, 1 - 10 moles, de preferencia 1 - 5 moles, por 1 mol de compuesto (8).

Esta reacción se realiza con preferencia en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, alcoholes tales como metanol, etanol, 1-propanol, 2-propanol, alcohol ter-butílico y similares; éteres tales como 1,4-dioxano, tetrahidrofurano, éter dietílico, dimetoxietano, éter ter-butilmetílico, éter diisopropílico, dimetiléter de etilenglicol y similares; ésteres tales como formiato de etilo, acetato de etilo, acetato de isopropilo, acetato de n-butilo y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, tricloroetileno y similares; hidrocarburos tales como n-hexano, benceno, tolueno y similares; amidas tales como formamida, N,N-dimetilformamida, N,N-dimetilacetamida y similares; nitrilos tales como acetonitrilo, propionitrilo y similares; sulfóxidos tales como dimetilsulfóxido y similares; sulfolano; hexametilfosforamida; y similares. Se pueden usar

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dos o más clases de estos solventes en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, -80 °C - 200 °C, con preferencia 0 °C - 150 °C.

El tiempo de reacción es, en general, 10 min - 48 h, con preferencia 15 min - 24 h.

Etapa 7

El compuesto (3) se puede producir por someter, por ejemplo, el compuesto (6) a una reacción de reducción de acuerdo con el método de producción del compuesto (2).

Etapa 8

El compuesto (BII) se puede producir por la reacción, por ejemplo, del compuesto (3) con el compuesto metálico orgánico (12).

Los ejemplos del compuesto metálico orgánico (12) incluyen reactivo de Grignard (por ejemplo, un compuesto representado por la fórmula: $R^3MgBr$), reactivo orgánico de litio (por ejemplo, un compuesto representado por la fórmula: $R^3Li$), reactivo orgánico de zinc (por ejemplo, un compuesto representado por la fórmula: $(R^3)_2Zn$), en donde $R^3$ es como se definió anteriormente y similares.

Dicho compuesto metálico orgánico se puede producir por un método conocido per se, por ejemplo, el método descrito en "Jikken Kagaku Kouza (The Chemical Society of Japan ed.), 4a edición, vol. 25, Synthesis by Organic Metal Reagent" pp. 9-449, Maruzen Press 1992 o un método análogo a este.

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La cantidad del compuesto metálico orgánico (12) que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (3).

Esta reacción se realiza en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, se pueden mencionar éteres tales como éter dietílico, tetrahidrofurano, 1,4-dioxano y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; y similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

El tiempo de reacción es, en general, 10 min - 48 h, con preferencia 15 min - 24 h.

La temperatura de reacción es, en general, -100 - 200 °C, con preferencia -80 - 150 °C.

Etapa 9

El compuesto (BII) se puede producir, por ejemplo, por el tratamiento del compuesto (4) con una base y la reacción del compuesto con el compuesto (13).

Los ejemplos de la base incluyen a las similares a la base descripta en la etapa 3.

La cantidad de base y compuesto (13) que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (4).

Esta reacción se realiza con preferencia en un solvente inerte para la reacción. Los ejemplos del solvente incluyen los similares al solvente descrito en la etapa 3.

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El tiempo de reacción es, en general, 10 min - 48 h, con preferencia 15 min - 24 h.

La temperatura de reacción es, en general, -100 - 100 °C, con preferencia -80 - 50 °C.

Como compuesto (13), se puede usar un producto disponible en el comercio o se puede producir a partir de un compuesto disponible en el comercio por un método conocido per se o un método análogo a este.

Etapa 10

El compuesto (BII) se puede producir por el tratamiento, por ejemplo, del compuesto (9) con una base y luego reacciona con el compuesto con el compuesto (13).

Los ejemplos de la base incluyen compuestos orgánicos de litio tal como n-butil-litio, sec-butil-litio, ter-butil-litio y similares.

La cantidad de base y compuesto (13) que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (9).

Esta reacción se realiza con preferencia en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, se pueden mencionar éteres tales como 1,4-dioxano, tetrahidrofurano, éter dietílico, éter ter-butilmetílico, éter diisopropílico, dimetiléter de etilenglicol y similares; hidrocarburos tales como n-hexano, n-pentano y similares; y similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

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El tiempo de reacción es, en general, 10 min - 48 h, con preferencia 15 min - 24 h.

La temperatura de reacción es, en general, -100 - 100 °C, con preferencia -80 - 50 °C.

Como compuesto (9), se puede usar un producto disponible en el comercio o se puede producir a partir de un compuesto disponible en el comercio por un método conocido per se o un método análogo a este.

Etapa 11

El compuesto (BV) se puede producir, por ejemplo, al someter el compuesto (BII) a una reacción de oxidación de acuerdo con etapa 2.

Etapa 12

El compuesto (BV) se puede producir por la reacción del compuesto (6) con el compuesto metálico orgánico (12) de acuerdo con, por ejemplo, la etapa 8.

Etapa 13

El compuesto (BV) se puede producir por la reacción de Friedel-Crafts del compuesto (4) y el compuesto (10)

Si bien esta reacción se realiza con preferencia por la adición de un catalizador ácido, cuando sea necesario, se puede realizar sin la adición de un catalizador ácido.

Los ejemplos del catalizador ácido usado para la reacción incluyen ácidos minerales tales como ácido sulfúrico, ácido fosfórico anhidro, ácido polifosfórico y similares, ácidos de Lewis tales como cloruro de aluminio, tetracloruro de estaño, tetracloruro de titanio, trifluoruro de boro, trietilaluminio, cloruro de dietilaluminio, cloruro

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de zinc y demás y similares. Con preferencia, se usan ácido polifosfórico, cloruro de aluminio, cloruro de dietilaluminio, cloruro de zinc y similares como catalizadores ácidos.

Un catalizador ácido se puede usar en cualquier cantidad equivalente, generalmente 0,1 - 50 moles, con preferencia 1 - 20 moles, por 1 mol de compuesto (4). N algunos casos, también se puede usar un catalizador ácido como un solvente.

La cantidad del compuesto (10) que se usa es, en general, 1 - 20 moles, con preferencia 1 - 10 moles, por 1 mol de compuesto (4).

Esta reacción se puede realizar sin solvente o después de disolver o suspender en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, se pueden mencionar hidrocarburos tales como n-hexano, benceno, tolueno y similares; éteres tales como 1,4-dioxano, tetrahidrofurano, éter dietílico, dimetoxietano, éter ter-butilmetílico, éter diisopropílico, dimetiléter de etilenglicol, 1,2-dicloroetano y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, tricloroetileno y similares; nitrohidrocarburos tales como nitrometano, nitrobenceno y similares; nitrilos tales como acetonitrilo, propionitrilo y similares; amidas tales como formamida, N,N-dimetilformamida, N,N-dimetilacetamida y similares; sulfóxidos tales como dimetilsulfóxido y similares; sulfolano; hexametilfosforamida; disulfuro de

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carbono; y similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

El tiempo de reacción es, en general, 10 min - 48 h, con preferencia 15 min - 24 h.

La temperatura de reacción es, en general, -100 - 300 °C, con preferencia 0 - 200 °C.

Como compuesto (10), se puede usar un producto disponible en el comercio o se puede producir a partir de un compuesto disponible en el comercio por un método conocido per se o un método análogo a este.

Etapa 14

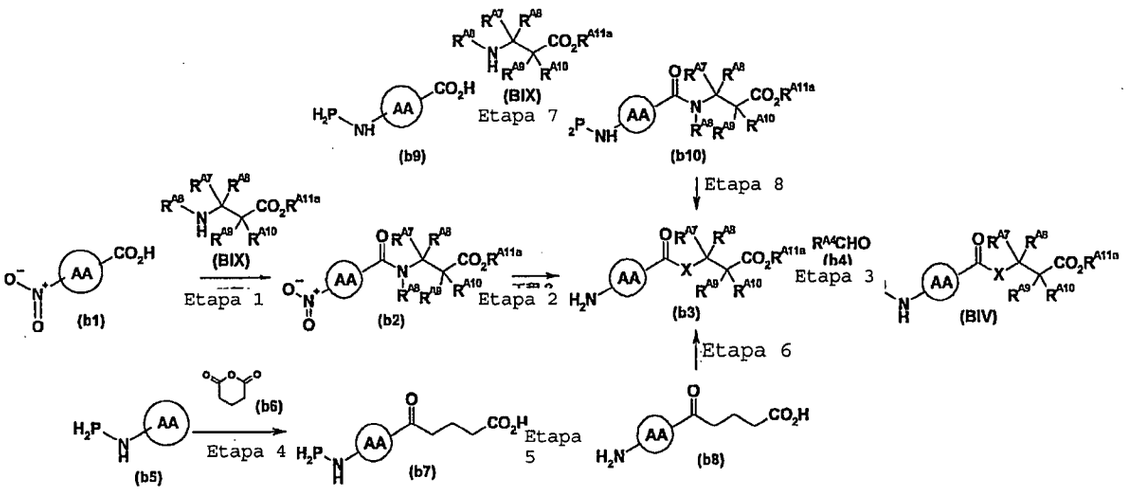
El compuesto (BV) se puede producir, por ejemplo, por la reacción del compuesto (11) con un reactivo metálico orgánico de acuerdo con etapa 8.

Como el compuesto (11), se puede usar un producto disponible en el comercio o se puede producir a partir de un compuesto disponible en el comercio por un método conocido per se o un método análogo a este.

El compuesto (BIV) que es un compuesto material de partida en Esquema de reacción A1 se puede producir, por ejemplo, por un método que se muestra en el siguiente esquema de reacción A3.

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Esquema de reacción A3




en donde P es un grupo protector de amino y otros símbolos son como se definieron anteriormente.

Etapa 1

El compuesto (b2) se puede producir, por ejemplo, por la condensación del compuesto (b1) y el compuesto (BIX) de acuerdo con el método de producción del compuesto (B1a) a partir del compuesto (BVIII).

Como compuesto (b1), se puede usar un producto disponible en el comercio o se puede producir a partir de un compuesto disponible en el comercio por un método conocido per se o un método análogo a este.

Etapa 2

El compuesto (b3) se puede producir al someter el compuesto (b2) a una reacción de reducción en presencia de un catalizador metálico y una fuente de hidrógeno. Dicha reacción de reducción se puede realizar de acuerdo con un método convencional en un solvente que no influencia adversamente la reacción.

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Los ejemplos del catalizador metálico incluyen paladio-carbón, negro de paladio, cloruro de paladio, óxido de platino, negro de platino, platino-paladio, Raney-níquel, Cobalto Raney y similares.

Los ejemplos de la fuente de hidrógeno incluyen gas hidrógeno, ácido fórmico, sal amina de ácido fórmico, sal fosfinato, hidrazina y similares.

Los ejemplos del solvente que no influencia adversamente la reacción incluye metanol, tetrahidrofurano, N,N-dimetilacetamida y similares.

La cantidad del catalizador metálico que se usa es, en general, 0,001 - 1000 moles, con preferencia 0,01 - 100 moles, por 1 mol de compuesto (b2).

La temperatura de reacción es, en general, -70 - 150 °C, con preferencia -20 - 100 °C.

El tiempo de reacción es, en general, 0,1 - 100 h, con preferencia 0,1 - 40 h.

Esta reacción también se puede realizar en presencia de un agente reductor en un solvente que no influencia adversamente la reacción.

Como agente reductor, se puede mencionar óxido férrico, zinc, estaño y similares y el compuesto (b3) se puede producir de acuerdo con la reacción descripta en "Jikken Kagaku Kouza (The Chemical Society of Japan ed.), 4t Edición, vol. 20. Organic Synthesis II Alcohol and Amine" pp. 279-280, Maruzen Press 1992 o un método análogo a este.

La cantidad del agente reductor que se usa es, en general, 0,1 - 20 moles por 1 mol de compuesto (b2).

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Los ejemplos del solvente que no influencia adversamente la reacción incluye alcoholes tales como metanol, etanol, propanol, isopropanol, butanol, isobutanol, ter-butanol y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, dimetoxietano y similares; ésteres tales como acetato de metilo, acetato de etilo, acetato de n-butilo, acetato de ter-butilo y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; y similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, -70 - 150 °C, con preferencia -20 - 100 °C.

El tiempo de reacción es, en general, 0,1 - 100 h, con preferencia 0,1 - 40 h.

Etapa 3

El compuesto (BIV) se puede producir, por ejemplo, por la reacción de aminación reductora de compuesto (b3) y compuesto (b4) de acuerdo con el método de producción del compuesto (B1a) a partir del compuesto (BV).

Como compuesto (b4), se puede usar un producto disponible en el comercio o se puede producir a partir de un compuesto disponible en el comercio por un método conocido per se o un método análogo a este.

Etapa 4

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Compuesto (b7) se puede producir por Friedel-Crafts reacción de compuesto (b5) y anhídrido glutárico (b6) por el método de síntesis descrito en el documento WO 2004/45616 o un método análogo a este.

Como compuesto (b5), se puede usar un producto disponible en el comercio o se puede producir a partir de un compuesto disponible en el comercio por un método conocido per se o un método análogo a este.

Etapa 5

El compuesto (b8) se puede producir por la eliminación del grupo protector a partir del compuesto (b7) por un método conocido per se, por ejemplo, el método descrito en Protective Groups in Organic Synthesis, Tercera edición, Wiley-Interscience (1999) o un método análogo a este.

Etapa 6

El compuesto (b3) ($R^{A7}$, $R^{A8}$, $R^{A9}$ y $R^{A10}$ son átomos de hidrógeno) se puede producir por la esterificación de compuesto (b8) por un método conocido per se, por ejemplo, el método descrito en Protective Groups in Organic Synthesis, Tercera edición, Wiley-Interscience (1999) o un método análogo a este.

Etapa 7

El compuesto (b10) se puede producir, por ejemplo, por la condensación del compuesto (b9) y el compuesto (BIX) de acuerdo con el método de producción del compuesto (B1a) a partir del compuesto (BVIII).

Como compuesto (b9), se puede usar un producto disponible en el comercio o se puede producir a partir de un

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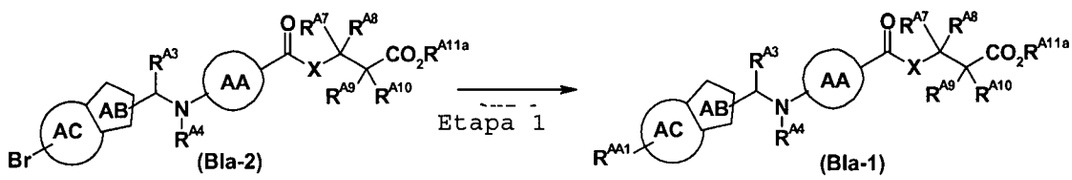
compuesto disponible en el comercio por un método conocido per se o un método análogo a este.

Etapa 8

El compuesto (b3) se puede producir, por ejemplo, por la eliminación del grupo protector a partir del compuesto (b10) de acuerdo con el método de la etapa 5.

De los compuestos (IA), un compuesto representado por la siguiente fórmula (BIa-1) [el compuesto (BIa-1)] se puede producir de acuerdo con el siguiente esquema de reacción A4.

Esquema de reacción A4




en donde $R^{AA1}$ es un grupo alquilo $C_{1-6}$, un grupo arilo $C_{6-14}$, un grupo heterocíclico aromático de 4 a 12 miembros (grupo unido por medio de un átomo de carbono del anillo), un grupo heterocíclico no aromático de 4 a 12 miembros (grupo unido por medio de un átomo de carbono del anillo) o un grupo ciano y otros símbolos como se definieron anteriormente.

Etapa 1

El compuesto (BIa-1) se puede producir, por ejemplo, por la reacción del compuesto (BIa-2) con un reactivo metálico orgánico o cianuro metálico en presencia de un catalizador metálico.

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Los ejemplos del catalizador metálico incluyen catalizador de paladio (por ejemplo, acetato de paladio (II), tris(dibenzilidenacetona)dipaladio (0), bis(dibenzilidenacetona)paladio (0), tetrakis(trifenilfosfino)paladio (0), aducto de [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio (II) diclorometano, bis(tris-ter-butilfosfino)paladio (0) etc.); catalizador de níquel (por ejemplo, tetrakis(trifenilfosfino)níquel (0), dicloro[1,2-bis(difenilfosfino)etano]níquel (II), dicloro[1,3-bis(difenilfosfino)propano]níquel (II), dicloro[1,4-bis(difenilfosfino)butano]níquel (II) etc.).

La cantidad del catalizador metálico que se usa es, en general, 0,01 - 1 mol, con preferencia 0,03 - 0,5 moles, por 1 mol de compuesto (BIa-2).

Los ejemplos del reactivo metálico orgánico incluyen ácido borónico, éster de boronato, reactivo de Grignard, reactivo de organoestaño, reactivo de organozinc y similares.

Los ejemplos del cianuro metálico incluyen cianuro de zinc y similares.

La cantidad del reactivo metálico orgánico o cianuro metálico que se usa es, en general, 1 - 100 moles, con preferencia 1 - 10 moles, por 1 mol de compuesto (BIa-2).

Esta reacción se puede realizar en presencia de una base según corresponda.

Los ejemplos de dicha base incluyen hidróxidos de metal alcalino tales como hidróxido de litio, hidróxido de sodio, hidróxido de potasio y similares; hidróxidos de metal

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alcalinotérreo tales como hidróxido de magnesio, hidróxido de calcio y similares; carbonatos de metal alcalino tales como carbonato de sodio, carbonato de potasio, carbonato de cesio y similares; carbonatos ácidos de metal alcalino tales como carbonato ácido de sodio, carbonato ácido de potasio y similares; alcóxido de metal alcalino que tiene un número de carbono de 1 a 6 tal como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares, y similares.

La cantidad de base que se usa es, en general, 1 - 100 moles, con preferencia 1 - 10 moles, por 1 mol de compuesto (BIa-2).

Esta reacción se puede realizar en presencia de un ligando según corresponda.

Los ejemplos de dichos ligandos incluyen ligando de fósforo (por ejemplo, trifenilfosfina, 1,3-bis(difenilfosfino)propano, 1,3-bis(difenilfosfino)propano, 2,2'-bis(difenilfosfino)-1,1'-binaftilo y 4,5-bis(difenilfosfino)-9,9-dimetilxanteno, etc.).

La cantidad del ligando que se usa es, en general, 0,01 - 2 moles, con preferencia 0,02 - 1 mol, por 1 mol de compuesto (BIa-2).

Esta reacción se realiza con preferencia en un solvente inerte para la reacción.

Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, se pueden mencionar alcoholes tales como metanol, etanol, propanol, isopropanol, butanol, ter-butanol y similares; éteres tales como 1,4-dioxano, tetrahidrofurano, éter dietílico, dimetoxietano,

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éter ter-butilmetílico, éter diisopropílico, dimetiléter de etilenglicol y similares; ésteres tales como formiato de etilo, acetato de etilo, acetato de n-butilo y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, tricloroetileno y similares; hidrocarburos tales como n-hexano, benceno, tolueno y similares; amidas tales como formamida, N,N-dimetilformamida, N,N-dimetilacetamida y similares; nitrilos tales como acetonitrilo, propionitrilo y similares; sulfóxidos tales como dimetilsulfóxido y similares; sulfolano; hexametilfosforamida; agua y similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, -100 - 180 °C, con preferencia -80 °C - 150 °C.

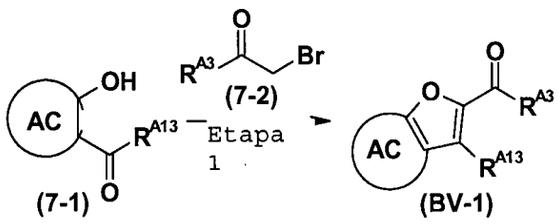
El tiempo de reacción es, en general, 0,1 h - 48 h, con preferencia 0,1 h - 24 h.

El compuesto (BIa-2) se puede producir, por ejemplo, de acuerdo con el método de producción del compuesto (BIa) en Esquema de reacción A1.

De los compuestos (BV) descritos en el Esquema de reacción A2, un compuesto representado por la siguiente la fórmula (BV-1) [compuesto (BV-1)] se puede producir de acuerdo con el siguiente esquema de reacción A5.

Esquema de reacción A5

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en donde cada símbolo es como se definió anteriormente.

Etapa 1

El compuesto (BV-1) se puede producir, por ejemplo, por la reacción del compuesto (7-1) con el compuesto (7-2) en presencia de una base.

Los ejemplos de la base incluyen hidróxidos de metal alcalino tales como hidróxido de litio, hidróxido de sodio, hidróxido de potasio y similares; hidróxidos de metal alcalinotérreo tales como hidróxido de magnesio, hidróxido de calcio y similares; carbonatos de metal alcalino tales como carbonato de sodio, carbonato de potasio, carbonato de cesio y similares; carbonatos ácidos de metal alcalino tales como carbonato ácido de sodio, carbonato ácido de potasio y similares; alcóxidos de metal alcalino que tienen 1 a 6 átomos de carbono tal como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares; hidruros metálicos tal como hidruro de sodio, hidruro de potasio y hidruro de calcio; bases orgánicas tal como 1,8-diazabiciclo[5,4,0]undec-7-eno (DBU), 1,5-diazabiciclo[4,3,0]non-5-eno (DBN), 1,4-diazabiciclo[2,2,2]octano (DABCO) y demás, y similares.

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La cantidad de base que se usa es, en general, 1 - 50 moles, con preferencia 1 - 20 moles, por 1 mol de compuesto (7-1).

La cantidad del compuesto (7-2) que se usa es, en general, 1 - 10 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (7-1).

Esta reacción se realiza con preferencia en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, se pueden mencionar alcoholes tales como metanol, etanol, 1-propanol, 2-propanol, alcohol ter-butílico y similares; éteres tales como 1,4-dioxano, tetrahidrofurano, éter dietílico, dimetoxietano, éter ter-butilmetílico, éter diisopropílico, dimetiléter de etilenglicol y similares; ésteres tales como formiato de etilo, acetato de etilo, acetato de isopropilo, acetato de n-butilo y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, tricloroetileno y similares; hidrocarburos tales como n-hexano, benceno, tolueno y similares; amidas tales como formamida, N,N-dimetilformamida, N,N-dimetilacetamida y similares; nitrilos tales como acetonitrilo, propionitrilo y similares; sulfóxidos tales como dimetilsulfóxido y similares; sulfolano; hexametilfosforamida y similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, -80 °C - 200 °C, con preferencia 0 °C - 150 °C.

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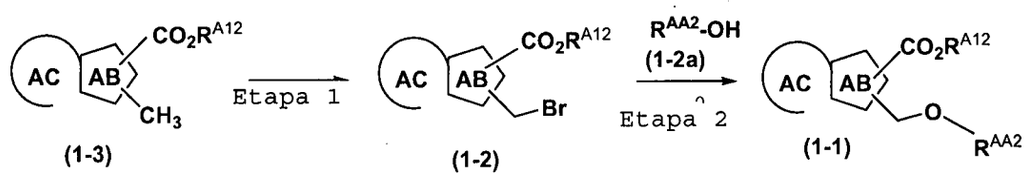
El tiempo de reacción es, en general, 10 min - 48 h, con preferencia 15 min - 24 h.

Compuesto (7-1) se puede producir por un método conocido per se o un método análogo a este.

Compuesto (7-2) se puede producir por un método conocido per se o un método análogo a este.

De los compuestos (1), un compuesto representado por la siguiente fórmula (1-1) [compuesto (1-1)] se puede producir de acuerdo con el siguiente esquema de reacción A6.

Esquema de reacción A6




en donde $R^{AA2}$ es un grupo alquilo $C_{1-6}$ y otros símbolos como se definieron anteriormente.

Etapa 1

El compuesto (1-2) se puede producir, por ejemplo, por la bromación del compuesto (1-3).

Los ejemplos de reactivo de bromación incluyen N-bromoamidas tales como N-bromosuccinimida, 1,3-dibromo-5,5-dimetilhidantoína y similares.

La cantidad del reactivo de bromación que se usa es, en general, 1 - 100 moles, con preferencia 1 - 10 moles, por 1 mol de compuesto (1-3).

Esta reacción se puede realizar en copresencia de un iniciador radical, según corresponda.

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Los ejemplos de dicho iniciador radical incluyen azobisisobutironitrilo, peróxido de benzoilo y similares.

La cantidad del iniciador radical que se usa es, en general, 0,001 - 10 moles, con preferencia 0,01 - 5 moles, por 1 mol de compuesto (1-3).

Esta reacción se realiza con preferencia en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, se pueden mencionar ésteres tales como formiato de etilo, acetato de etilo, acetato de n-butilo y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, tricloroetileno y similares; nitrilos tales como acetonitrilo, propionitrilo y demás y similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, -100 - 180 °C, con preferencia -80 °C - 150 °C.

El tiempo de reacción es, en general, 0,1 h - 48 h, con preferencia 0,1 h - 24 h.

Compuesto (1-3) se puede producir por un método conocido per se o un método análogo a este.

Etapa 2

El compuesto (1-1) se puede producir, por ejemplo, por la reacción del compuesto (1-2) con un alcóxido de metal alcalino.

En forma alternativa, el compuesto (1-1) también se puede producir, por ejemplo, por la reacción del compuesto (1-2) con el compuesto (1-2a) en presencia de una base.

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Los ejemplos del alcóxido de metal alcalino incluyen metóxido de sodio, metóxido de potasio, etóxido de sodio, etóxido de potasio y similares.

La cantidad de alcóxido de metal alcalino que se usa es, en general, 1 - 50 moles, con preferencia 1 - 10 moles, por 1 mol de compuesto (1-2).

Los ejemplos de la base incluyen carbonatos de metal alcalino tales como carbonato de sodio, carbonato de potasio, carbonato de cesio y similares; carbonatos ácidos de metal alcalino tales como carbonato ácido de sodio, carbonato ácido de potasio y similares; hidruros metálicos tal como hidruro de sodio, hidruro de potasio y hidruro de calcio y similares.

La cantidad de base que se usa es, en general, 1 - 50 moles, con preferencia 1 - 10 moles, por 1 mol de compuesto (1-2).

La cantidad del compuesto (1-2a) que se usa es, en general, 1 - 50 moles, con preferencia 1 - 10 moles, por 1 mol de compuesto (1-2).

Esta reacción se realiza con preferencia en un solvente inerte para la reacción. Dicho solvente no está particularmente limitado siempre que la reacción proceda y, por ejemplo, se pueden mencionar alcoholes tales como metanol, etanol, 1-propanol, 2-propanol, alcohol ter-butílico y similares; éteres tales como 1,4-dioxano, tetrahidrofurano, éter dietílico, dimetoxietano, éter ter-butilmetílico, éter diisopropílico, dimetiléter de etilenglicol y similares; ésteres tales como formiato de etilo, acetato de etilo, acetato de isopropilo, acetato de n-butilo y similares;

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hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, tricloroetileno y similares; hidrocarburos tales como n-hexano, benceno, tolueno y similares; amidas tales como formamida, N,N-dimetilformamida, N,N-dimetilacetamida y similares; nitrilos tales como acetonitrilo, propionitrilo y similares; sulfóxidos tales como dimetilsulfóxido y similares; sulfolano; hexametilfosforamida y similares. Se pueden usar dos o más clases de estos solventes en una mezcla en una proporción apropiada.

En esta reacción, se pueden añadir yoduros de metal alcalino tales como yoduro de sodio, yoduro de potasio y similares como promotor de la reacción en una cantidad de generalmente 1 - 50 moles, con preferencia 1 - 10 moles, por 1 mol de compuesto (1-2).

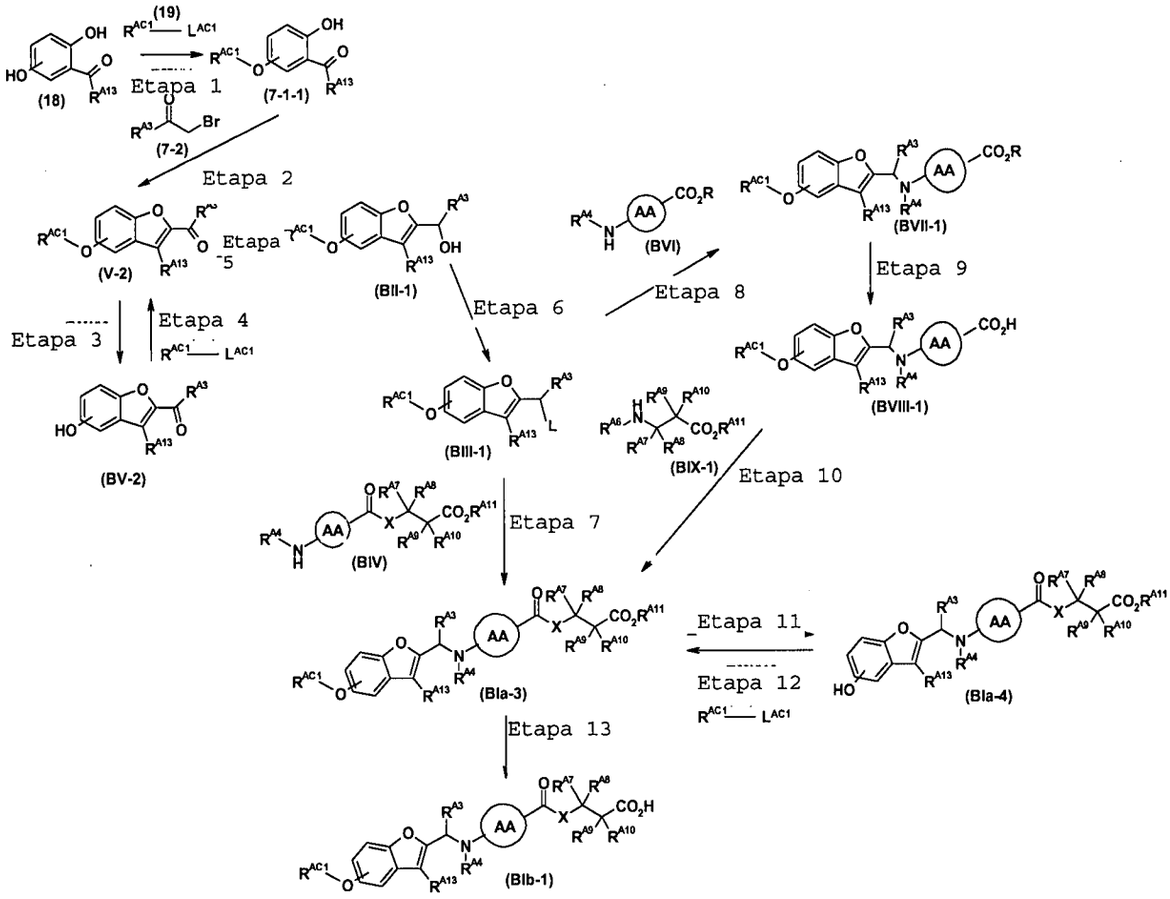
La temperatura de reacción es, en general, -80 °C - 200 °C, con preferencia 0 °C - 150 °C. El tiempo de reacción es, en general, 0,1 h - 48 h, con preferencia 0,1 h - 24 h.

El compuesto (1-2a) se puede producir por un método conocido per se o un método análogo a este.

En el compuesto (BIa) del Esquema de reacción A1, un compuesto representado por la siguiente fórmula (BIa-3) [compuesto (BIa-3)] y un compuesto representado por la fórmula (BIa-4) [compuesto (BIa-4)] y en el compuesto (BIb) de Esquema de reacción A1, un compuesto representado por la siguiente fórmula (BIb-1) [compuesto (BIb-1)] se puede producir, por ejemplo, por los métodos mostrados en el siguiente esquema de reacción A7.

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Esquema de reacción A7




en donde $R^{AC1}$ es

(1) alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) grupo carboxi,

(c) grupo alcoxi $C_{1-6}$,

(d) grupo cicloalquilo $C_{3-6}$,

(e) grupo alcoxi $C_{1-6}$-carbonilo opcionalmente sustituido con 1 a 3 grupos arilo $C_{6-14}$,

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(f) grupo amino opcionalmente mono o disustituido con sustituyentes seleccionados del grupo alquilo $C_{1-6}$ y grupo alcoxi $C_{1-6}$-carbonilo,

(g) grupo heterocíclico aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(i) átomo de halógeno y

(ii) grupo alquilo $C_{1-6}$,

(h) grupo heterocíclico no aromático de 4 a 12 miembros, grupo heterocíclico no aromático opcionalmente sustituido con 1 a 3 grupos alquilo $C_{1-6}$,

(i) grupo alquilsulfonilo $C_{1-6}$,

(j) grupo alquiltio $C_{1-6}$ y

(k) grupo hidroxi;

(2) grupo aralquilo $C_{7-13}$;

(3) grupo arilo $C_{6-14}$;

(4) grupo alquil $C_{1-6}$-carbonilo;

(5) grupo heterocíclico aromático de 4 a 12 miembros opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(i) grupo alquilo $C_{1-6}$ opcionalmente sustituido con 1 a 3 átomos de halógeno y

(ii) grupo ciano;

(6) grupo heterociclil-oxi no aromático de 4 a 12 miembros o un grupo hidroxi,

y otros símbolos como se definieron anteriormente.

Los ejemplos del "grupo saliente" para $L^{AC1}$ incluyen átomo de flúor, átomo de cloro, átomo de bromo, átomo de

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yodo, grupo bencensulfoniloxi, grupo p-toluensulfoniloxi, grupo metansulfoniloxi, grupo trifluorometansulfoniloxi y similares.

Etapa 1

En esta etapa, por ejemplo, el compuesto (7-1-1) se puede producir por la reacción del compuesto (18) con el compuesto (19).

Cuando $L^{AC1}$ es un grupo saliente, esta reacción se realiza en presencia de una base en un solvente que no influencia adversamente la reacción.

Los ejemplos de la base incluyen aminas tal como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, 4-dimetilaminopiridina y similares; sales de metal alcalino tales como carbonato ácido de sodio, carbonato de sodio, carbonato de potasio, fosfato de tripotasio y similares; hidróxido de metal alcalino tal como hidróxido de sodio, hidróxido de potasio, hidróxido de litio y similares; hidróxido de metal alcalinotérreo tal como hidróxido de magnesio, hidróxido de calcio, hidróxido de bario y similares; hidruros metálicos tal como hidruro de potasio, hidruro de sodio y similares; alcóxido $C_{1-6}$ de metal alcalino tal como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y demás y similares.

La cantidad de base que se usa es, en general, 1 - 1000 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (18).

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La cantidad del compuesto (19) que se usa es, en general, 1 - 1000 moles, con preferencia 1 - 10 moles, por 1 mol de compuesto (18).

Los ejemplos de solvente que no influencia adversamente la reacción incluyen éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida y similares; sulfóxidos tales como dimetilsulfóxido y similares; cetonas tales como acetona y similares; acetonitrilo; agua. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, -80 °C a 150 °C, con preferencia -10 °C a 100 °C.

El tiempo de reacción es, en general, 0,5 - 20 h.

Cuando $L^{AC1}$ es un grupo hidroxi, esta reacción se realiza por un método conocido per se, por ejemplo, el método descrito en Synthesis, página 1 (1981) o un método análogo a este. Es decir, esta reacción se realiza generalmente en presencia de un compuesto orgánico de fósforo y electrófilo en un solvente que no influencia adversamente la reacción.

Los ejemplos de compuesto orgánico de fósforo incluye trifenilfosfina, tributilfosfina y similares.

Los ejemplos de electrófilo incluyen azodicarboxilato de dietilo, azodicarboxilato de diisopropilo, 1,1'-azodicarbonildipiperidina y similares.

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La cantidad del compuesto orgánico de fósforo y electrófilo que se usa es, en general, 1 - 1000 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (18).

La cantidad del compuesto (19) que se usa es, en general, 1 - 1000 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (18).

Como solvente que no influencia adversamente la reacción, se pueden mencionar los similares a los mencionados anteriormente.

La temperatura de reacción es, en general, -80 - 150 °C, con preferencia -10 - 100 °C.

El compuesto (18) y el compuesto (19) se pueden producir de acuerdo con un método conocido per se.

Etapa 2

En esta etapa, por ejemplo, el compuesto (7-1-1) se hace reaccionar con el compuesto (7-2) en presencia de una base para dar compuesto (V-2).

Esta reacción se realiza de la misma manera que en el Esquema de reacción A5, etapa 1.

El compuesto (7-2) se puede producir de acuerdo con un método conocido per se.

Etapa 3

En esta etapa, por ejemplo, $R^{AC1}$ del compuesto (V-2) se elimina para dar el compuesto (BV-2).

Cuando $R^{AC1}$ es un grupo bencilo, esta reacción se puede realizar, por ejemplo, en presencia de un catalizador metálico tal como paladio-carbón, negro de paladio, complejo de paladio-carbón etilendiamina, cloruro de paladio, óxido de

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platino, negro de platino, platino-paladio, Raney-níquel, cobalto Raney y similares y una fuente de hidrógeno en un solvente que no influencia adversamente la reacción.

La cantidad del catalizador metálico que se usa es, en general, 0,001 - 1000 moles, con preferencia 0,01 - 100 moles, por 1 mol de compuesto (V-2).

Los ejemplos de la fuente de hidrógeno incluyen gas hidrógeno, ácido fórmico, sal de amina ácido fórmico, sal fosfinato, hidrazina y similares.

Los ejemplos del solvente que no influencia adversamente la reacción incluyen alcoholes tales como metanol, etanol, propanol, 2-propanol, 2-metoxietanol, butanol, isobutanol, ter-butanol y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, 1,2-dicloroetano, 1,1,2,2-tetracloroetano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; acetato de etilo, ácido acético y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, 0 - 120 °C, con preferencia 10 - 80 °C.

El tiempo de reacción es, en general, 0,5 - 100 h.

Etapa 4

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En esta etapa, por ejemplo, el compuesto (V-2) se puede producir por la reacción del compuesto (BV-2) con el compuesto (19). Esta etapa se realiza de la misma manera que en esta reacción, etapa 1.

Etapa 5

En esta etapa, por ejemplo, el compuesto (BII-1) se puede producir al someter el compuesto (V-2) a una reacción de reducción. Esta reacción se realiza de la misma manera que en Esquema de reacción 1, etapa 1.

Etapa 6

En esta etapa, por ejemplo, el compuesto (BIII-1) se puede producir por la conversión del grupo hidroxi del compuesto (BII-1) al grupo saliente (L). Esta reacción se realiza de la misma manera que en Esquema de reacción A1, etapa 1.

Etapa 7

En esta etapa, por ejemplo, el compuesto (BIa-3) se puede producir por la reacción del compuesto (BIII-1) con el compuesto (BIV) en presencia de una base. Esta reacción se realiza de la misma manera que en Esquema de reacción A1, etapa 2.

Etapa 8

En esta etapa, por ejemplo, el compuesto (BVII-1) se puede producir por la reacción del compuesto (BIII-1) con el compuesto (BVI) en presencia de una base. Esta reacción se realiza de la misma manera que en Esquema de reacción A1, etapa 4.

Etapa 9

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En esta etapa, por ejemplo, el compuesto (BVIII-1) se puede producir por hidrólisis del éster del compuesto (BVII-1). Esta reacción se realiza de la misma manera que en Esquema de reacción A1, etapa 6.

Etapa 10

En esta etapa, por ejemplo, el compuesto (BIa-3) se puede producir por la condensación del compuesto (BVIII-1) y el compuesto (BIX-1). Esta reacción se realiza de la misma manera que en el Esquema de reacción A1, etapa 7.

Como compuesto (BIX-1), se puede usar un producto disponible en el comercio o se puede producir a partir de un compuesto disponible en el comercio por un método conocido per se o un método análogo a este.

Etapa 11

En esta etapa, por ejemplo, el compuesto (BIa-4) se puede producir por eliminación de $R^{AC1}$ a partir del compuesto (BIa-3). Esta etapa se realiza de la misma manera que en esta reacción, etapa 3.

Etapa 12

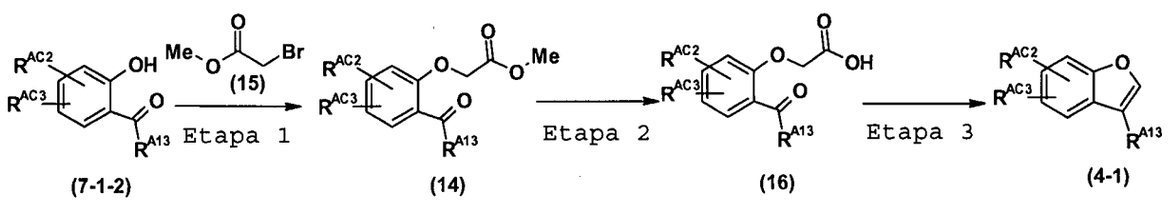
En esta etapa, por ejemplo, el compuesto (BIa-3) se puede producir por la reacción del compuesto (BIa-4) con el compuesto (19). Esta etapa se realiza de la misma manera que en esta reacción, etapa 1.

Etapa 13

En esta etapa, por ejemplo, el compuesto (BIb-1) se puede producir por hidrólisis del éster del compuesto (BIa-3) de acuerdo con el método de producción del compuesto (BVIII).

El compuesto (4-1) que es un compuesto de material de partida de Esquema de reacción A2 se puede producir, por ejemplo, de acuerdo con el método mostrado en el siguiente esquema de reacción A8.

Esquema de reacción A8




en donde $R^{AC2}$ y $R^{AC3}$ son un sustituyente que tiene opcionalmente el anillo anteriormente mencionado y otros símbolos como se definieron anteriormente.

Etapa 1

En esta etapa, por ejemplo, el compuesto (14) se puede producir por la reacción del compuesto (7-1-2) con el compuesto (15) en condiciones básicas. Esta reacción se realiza de la misma manera que en el Esquema de reacción A5, etapa 1.

Etapa 2

En esta etapa, por ejemplo, el compuesto (16) se puede producir por hidrólisis del éster del compuesto (14) de acuerdo con el método de producción del compuesto (BVIII) en el Esquema de reacción A1.

Etapa 3

En esta etapa, por ejemplo, el compuesto (4-1) se puede producir por la reacción del compuesto (16) en anhídrido acético.

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En esta etapa, se puede usar acetato de sodio como un aditivo.

La cantidad de acetato de sodio que se usa es, en general, 1 - 1000 moles, con preferencia 1 - 10 moles, por 1 mol de compuesto (16).

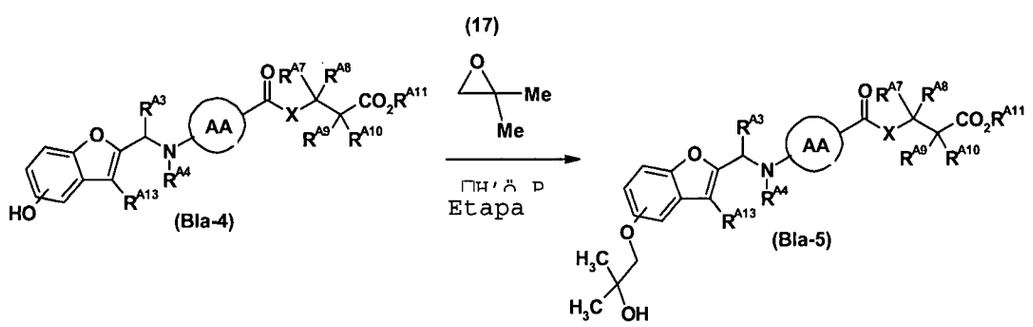
La temperatura de reacción es, en general, -80 - 200 °C, con preferencia -10 - 150 °C.

El tiempo de reacción es, en general, 0,5 - 20 h.

El compuesto (7-1-2) y el compuesto (15) se puede producir de acuerdo con un método conocido per se.

En el compuesto (BIa-3) del Esquema de reacción A7, un compuesto representado por la siguiente fórmula (BIa-5) [compuesto (BIa-5)] se puede producir, por ejemplo, por el método mostrado en el siguiente esquema de reacción A9.

Esquema de reacción A9




en donde los símbolos son como se definieron anteriormente.

Etapa 1

En esta etapa, por ejemplo, el compuesto (BIa-5) se puede producir por la reacción del compuesto (BIa-4) con el compuesto (17).

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Esta reacción se realiza en presencia de una base en un solvente que no influencia adversamente la reacción.

Los ejemplos de la base incluyen aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, 4-dimetilaminopiridina y similares; sales de metal alcalino tales como carbonato ácido de sodio, carbonato de sodio, carbonato de potasio y similares; hidróxidos de metal alcalino tales como hidróxido de sodio, hidróxido de potasio, hidróxido de litio y similares; hidróxidos de metal alcalinotérreo tales como hidróxido de magnesio, hidróxido de calcio, hidróxido de bario y similares; hidruros metálicos tal como hidruro de potasio, hidruro de sodio y similares; alcóxidos $C_{1-6}$ de metal alcalino tales como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y demás y similares.

La cantidad de base que se usa es, en general, 1 - 50 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (BIa-4).

La cantidad del compuesto (17) que se usa es, en general, 1 - 50 moles, con preferencia 1 - 5 moles, por 1 mol de compuesto (BIa-4).

En esta reacción, también se puede añadir yoduro de sodio o yoduro de potasio al solvente.

La cantidad de yoduro de sodio o yoduro de potasio que se usa es, en general, 1 - 100 moles, con preferencia 1 - 10 moles, por 1 mol de compuesto (BIa-4).

Los ejemplos del solvente que no influencia adversamente la reacción incluye éteres tales como éter dietílico,

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tetrahidrofurano, dioxano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; amidas tales como N,N-dimetilformamida y similares; sulfóxidos tales como dimetilsulfóxido y similares; cetonas tales como acetona y similares; acetonitrilo; agua. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, 0 - 150 °C, con preferencia 0 - 100 °C.

El tiempo de reacción es, en general, 0,5 - 100 h.

El compuesto (BIa-4) se puede producir de acuerdo con el Esquema de reacción A7.

El compuesto (17) se puede producir de acuerdo con un método conocido per se.

El compuesto (I) obtenido de este modo y el compuesto (IA) se pueden aislar y purificar por medios de separación y purificación conocidos, por ejemplo, concentración, concentración a presión reducida, extracción con solvente, cristalización, recristalización, transferencia de fase, cromatografía y similares.

Además, cuando el compuesto (I) y el compuesto (IA) se obtienen como compuestos libres, estos se pueden convertir en sales objeto por un método conocido per se o un método análogo a este. Cuando se obtienen como sales, se pueden convertir en formas libres u otras sales objeto por un método conocido per se o un método análogo a este.

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Cuando el compuesto (I) o el compuesto (IA) contiene un isómero óptico, un estereoisómero, un regioisómero o un rotámero, estos también están abarcados en el compuesto (I) y el compuesto (IA) y se pueden obtener como un solo producto de acuerdo con los métodos de síntesis y separación conocidos *per se*. Por ejemplo, cuando el compuesto (I) y el compuesto (IA) tienen un isómero óptico, un isómero óptico resuelto a partir de este compuesto también está abarcado en el compuesto (I) y compuesto (IA).

El isómero óptico se puede preparar de acuerdo con un método conocido per se. En forma específica, se usa un intermediario de síntesis ópticamente activo o el producto racemato final se somete a resolución óptica de acuerdo con un método convencional para dar un isómero óptico.

El método de resolución óptica puede ser un método conocido *per se*, tal como un método de recristalización fraccionada, un método de columna quiral, un método de diastereómero, etc.

1) Método de recristalización fraccionada

Un método en donde se forma una sal de un racemato con compuesto ópticamente activo (por ejemplo, (+) ácido mandélico, (-)ácido mandélico, (+)ácido tartárico, (-)ácido tartárico, (+)-1-fenetilamina, (-)-1-fenetilamina, zinconina, (-)-zinconidina, brucina, etc.), que se separa por un método de recristalización fraccionada y si se desea, una etapa de neutralización para dar un isómero óptico libre.

2) Método de columna quiral

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Un método en donde se aplica un racemato o una de sus sales a una columna para la separación de un isómero óptico (una columna quiral) para permitir la separación. En el caso de una cromatografía líquida, por ejemplo, se aplica una mezcla de isómeros ópticos a una columna quiral tal como ENANTIO-OVM (fabricado por Tosoh Corporation), serie CHIRAL (fabricado por Daicel Chemical Industries, Ltd.) y similares y desarrollados con agua, varios buffer (por ejemplo, buffer fosfato, etc.) y solventes orgánicos (por ejemplo, etanol, metanol, isopropanol, acetonitrilo, ácido trifluoroacético, dietilamina etc.) solos o en una mezcla para separar el isómero óptico. En el caso de una cromatografía gaseosa, por ejemplo, se usa una columna quiral tal como CP-Chirasil-DeX CB (fabricado por GL Sciences Inc.) y similares para permitir la separación.

3) Método de diastereómeros

Un método en donde se prepara una mezcla racémica en una mezcla diastereomérica por reacción química con un reactivo ópticamente activo, que se obtiene en una sustancia única con un medio de separación típica (por ejemplo, un método de recristalización fraccionada, un método de cromatografía etc.) y similares y se somete a un tratamiento químico tal como hidrólisis y similares para separar un residuo del reactivo ópticamente activo, por el cual se obtiene un isómero óptico. Por ejemplo, cuando el compuesto (I) o el compuesto (IA) contiene un grupo hidroxi o amino primario o secundario en una molécula, el compuesto y un ácido orgánico ópticamente activo (por ejemplo, MTPA [ácido α-metoxi-α-

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(trifluorometil)fenilacético], ácido (-)-mentoxiacético etc.) y similares se someten a una reacción de condensación para dar diastereómeros el compuesto éster o el compuesto amida, respectivamente. Cuando el compuesto (I) tiene un grupo carboxilo, este compuesto y una amina ópticamente activa o un alcohol ópticamente activo se someten a la reacción de condensación para dar diastereómeros del compuesto amida o el compuesto éster, respectivamente. El diastereómero separado se convierte en un isómero óptico del compuesto original por hidrólisis ácida o hidrólisis de base.

Ejemplos

La presente invención se explica con más detalle a continuación por referencia a los Ejemplos, Ejemplos experimentales y Ejemplos de formulación, que no se interpretan como limitativo.

El espectro $^{1}$H-RMN se midió usando tetrametilsilano como el estándar interno y Varian Gemini 200 (200 MHz), 300 (300 MHz), espectrómetros Bruker 300 (300 MHz) y todos los valores $\delta$ se muestran en ppm. A menos que se especifique de otro modo, los valores numéricos mostrados para los solventes mixtos son relaciones de mezcla de volumen de solventes respectivos. A menos que se especifique de otro modo, % significa % en peso. Además, a menos que se especifique de otro modo, la relación de solvente de elución en cromatografía de gel de sílice significa una relación de mezcla de volumen. La temperatura ambiente (temperatura ambiente) en la presente memoria descriptiva es una temperatura de aproximadamente 20 °C a aproximadamente 30 °C.

Cada símbolo de los Ejemplos significa lo siguiente.

DMSO: dimetilsulfóxido,

$CDCl_3$: cloroformo deuterado,

s: singulete,

d: doblete,

t: triplete,

q: cuarteto,

dd: doblete doble,

dt: triplete doble,

quint: quinteto,

m: multiplete,

brs: ancho,

J: constante de acoplamiento

Los análisis LC/MS de los Ejemplos se realizaron en las siguientes condiciones.

Dispositivo de medición: Sistema LC/MS Waters

HPLC: Agilent HP1100

MS: Micromass ZMD

columna: CAPCELL PAK c18UG120 S-3 μm, 1,5×35 mm (fabricada por Shiseido Co., Ltd.)

solvente: SOLUCIÓN A; 0,05% de solución de ácido trifluoroacético acuoso, SOLUCIÓN B; 0,04% de solución de ácido trifluoroacético y acetonitrilo

ciclo de gradiente: 0 min. (SOLUCIÓN A/SOLUCIÓN B = 90/10), 2,00 min. (SOLUCIÓN A/SOLUCIÓN B = 5/95), 2,75 min. (SOLUCIÓN A/SOLUCIÓN B = 5/95), 2,76 min. (SOLUCIÓN A/SOLUCIÓN B = 90/10), 3,60 min. (SOLUCIÓN A/SOLUCIÓN B = 90/10)

volumen de inyección: 2 μL,

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velocidad de flujo: 0,5 mL/min,

método de detección: UV 220 nm,

método de ionización en condiciones MS: ESI

La purificación por HLPC preparativa de los Ejemplos se realizó en las siguientes condiciones.

instrumento: Gilson Inc., sistema de purificación de alto rendimiento

columna: YMC CombiPrep ODS-A S-5 µm, 50x20 mm o CombiPrep Hidrosfere C18 S-5 µm, 50x20 mm

solvente: SOLUCIÓN A; 0,1% de solución acuosa de ácido trifluoroacético, SOLUCIÓN B; 0,1% de solución de ácido trifluoroacético y acetonitrilo

ciclo de gradiente: 0 min. (SOLUCIÓN A/SOLUCIÓN B = 95/5), 1,00 min. (SOLUCIÓN A/SOLUCIÓN B = 95/5), 5,20 min. (SOLUCIÓN A/SOLUCIÓN B = 5/95), 6,40 min. (SOLUCIÓN A/SOLUCIÓN B = 5/95), 6,50 min. (SOLUCIÓN A/SOLUCIÓN B = 95/5), 6,60 min. (SOLUCIÓN A/SOLUCIÓN B = 95/5) o 0 min. (SOLUCIÓN A/SOLUCIÓN B = 98/2), 1,00 min. (SOLUCIÓN A/SOLUCIÓN B = 98/2), 5,00 min. (SOLUCIÓN A/SOLUCIÓN B = 0/100), 6,40 min. (SOLUCIÓN A/SOLUCIÓN B = 0/100), 6,50 min. (SOLUCIÓN A/SOLUCIÓN B = 98/2), 6,60 min. (SOLUCIÓN A/SOLUCIÓN B = 98/2)

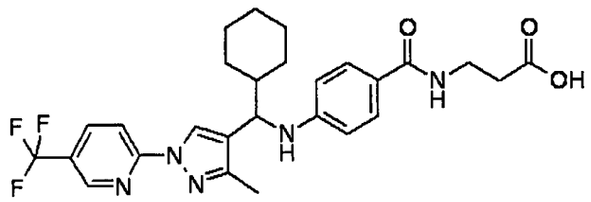
velocidad de flujo: 20 mL/min,

método de detección: UV 220 nm

Ejemplo 1

Ácido 3-[({4-[(ciclohexil{3-metil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

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(1) 3-[(4-nitrobenzoil)amino]propanoato de etilo

A una mezcla de ácido 4-nitrobenzoico (16,7 g), clorhidrato de éster etílico de β-alanina (18,4 g), monidrato de 1-hidroxibenzotriazol (18,4 g), trietilamina (16,7 mL) y N,N-dimetilformamida (200 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (23,0 g) y la mezcla se agitó a temperatura ambiente durante 8 h. La mezcla de reacción se vertió en agua y la mezcla se extrajo con acetato de etilo. El extracto se lavó con ácido clorhídrico 1 N y carbonato ácido de sodio acuoso saturado, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido blanco. La recristalización en acetato de etilo-hexano dio el compuesto objeto del título (26,6 g, 100%) en forma de cristales blancos.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,29 (t, J = 7,2 Hz, 3 H), 2,68 (t, J = 6,1 Hz, 2 H), 3,76 (q, J = 6,1 Hz, 2 H), 4,19 (q, J = 7,1 Hz, 2H), 7,03 (br. s., 1 H), 7,93 (d, J = 9,1 Hz, 2 H), 8,29 (d, J = 8,7 Hz, 2 H).

(2) 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo

Una mezcla de 3-[(4-nitrobenzoil)amino]propanoato de etilo (26,6 g) sintetizada con anterioridad, paladio sobre carbón al 5% (8,9 g), tetrahidrofurano (150 mL) y etanol (150

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mL) se agitó a temperatura ambiente durante la noche bajo una atmósfera de hidrógeno. El paladio sobre carbón al 5% se filtró y el filtrado se concentró a presión reducida para dar un sólido blanco. La recristalización en acetato de etilo-éter diisopropílico dio el compuesto objeto del título (22,6 g, 95%) en forma de cristales blancos.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,27 (t, J = 7,2 Hz, 3H), 2,63 (t, J = 6,0 Hz, 2 H), 3,70 (q, J = 6,0 Hz, 2 H), 3,94 (br. s., 2 H), 4,17 (q, J = 7,2 Hz, 2 H), 6,66 (d, J = 8,7 Hz, 2 H), 7,60 (d, J = 8,7 Hz, 2 H).

(3) 3-metil-1H-pirazol-4-carboxilato de metilo

Una mezcla de acetoacetato de metilo (30,0 g) y dimetilformamida dimetilacetal (34,7 mL) se agitó a 100 °C durante 12 h y la mezcla se dejó enfriar. Etanol (500 mL) y monohidrato de hidrazina (12,6 mL) se añadieron a la mezcla de reacción a temperatura ambiente y la mezcla se calentó a reflujo durante 12 h. La mezcla se dejó enfriar y se concentró a presión reducida. Se añadió agua al residuo y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida para dar el compuesto objeto del título (22,3 g, 61%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,56 (s, 3H), 3,84 (s, 3H), 7,96 (s, 1H).

(4) 3-metil-1-fenil-1H-pirazol-4-carboxilato de metilo

A una solución de 3-metil-1H-pirazol-4-carboxilato de metilo (5,3 g) sintetizada con anterioridad en dimetilformamida (70 mL) se añadió hidruro de sodio (1,9 g, 60% en aceite) a 0 °C y la mezcla se agitó durante 10 min. Se

agregó 2-cloro-5-trifluorometilpiridina (7,5 g) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió solución acuosa de cloruro de amonio a la mezcla de reacción y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:10, relación en volumen) para dar el compuesto objeto del título (3,3 g, 31%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,57 (s, 3 H), 3,87 (s, 3 H), 7,97 - 8,17 (m, 2 H), 8,63 - 8,74 (m, 1 H), 9,00 (s, 1 H).

(5) 3-metil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído

El 3-metil-1-fenil-1H-pirazol-4-carboxilato de metilo (3,3 g) sintetizado con anterioridad se disolvió en tetrahidrofurano (10 mL) y la solución se añadió gota a gota a una solución (20 mL) de hidruro de litio y aluminio (0,45 g) en tetrahidrofurano a 0 °C. La mezcla de reacción se agitó a 0 °C durante 30 min y cuidadosamente se añadió agua (0,45 mL) gota a gota. Por otra parte, se añadió solución acuosa 1 N de hidróxido de sodio (2,3 mL) y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se filtró a través de celite y el residuo se lavó con tetrahidrofurano (30 mL). Los extractos se combinaron, se secaron sobre sulfato de magnesio y se concentraron a presión reducida. El residuo se disolvió en tolueno (50 mL), se añadió dióxido de manganeso (8,8 g) y la mezcla se calentó a

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reflujo durante 1 h en condiciones de deshidratación. Después de enfriar, se filtró dióxido de manganeso y el residuo se evaporó a presión reducida para dar el compuesto objeto del título (2,6 g, 87%) en forma de un sólido amarillo pálido.
$^1$H RMN (300 MHz, $CDCl_3$) δ 2,57 (s, 3 H), 7,97 - 8,17 (m, 2 H), 8,63 - 8,74 (m, 1 H), 9,00 (s, 1 H), 9,95 (s, 1 H).
(6) ciclohexil{3-metil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol

A una solución de 3-metil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído (2,6 g) sintetizada con anterioridad en tetrahidrofurano (40 mL) se añadió gota a gota solución 1 M de bromuro de ciclohexilmagnesio-tetrahidrofurano (15 mL) a 0 °C. Después de agitar a 0 °C durante 1 h, se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (2,0 g, 36%) en forma de un sólido incoloro.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,93 (m, 11 H), 2,36 (s, 3 H), 3,62 (br. s., 1 H), 4,44 (dd, J = 7,2, 3,4 Hz, 1 H), 7,91 - 8,07 (m, 2 H), 8,43 (s, 1 H), 8,63 (s, 1 H).
(7) ácido 3-[({4-[(ciclohexil{3-metil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

A una solución (10 mL) de ciclohexil{3-metil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,75

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g) sintetizada con anterioridad en tetrahidrofurano se añadió cloruro de tionilo (0,24 mL) a temperatura ambiente y la mezcla se agitó durante 30 min. La mezcla de reacción se vertió en solución acuosa de hidrógeno-carbonato de sodio a 0 °C y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (15 mL) y se agregaron yoduro de sodio (0,63 g), carbonato de sodio (0,45 g) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,75 g) sintetizado en el Ejemplo 1, (2). La mezcla se agitó a 80 °C durante la noche y se dejó enfriar. A continuación, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título en una forma de éster etílico (876 mg). Esto se disolvió en etanol (4 mL), se añadió solución acuosa 1 N de hidróxido de sodio (4 mL) a temperatura ambiente y la mezcla se agitó durante 1 h. El etanol se evaporó a presión reducida y se añadió ácido clorhídrico 1 N (4 mL) añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,78 g, 70%) en forma de un sólido blanco.

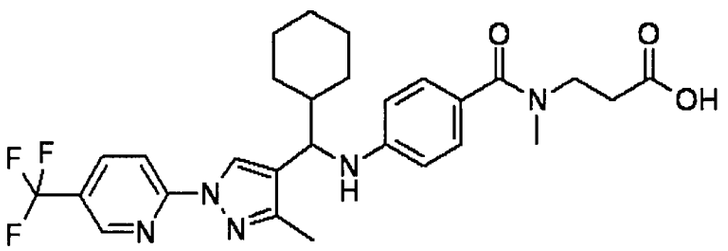
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,81 - 2,23 (m, 11 H), 2,34 (s, 3 H), 2,50 - 2,68 (m, 2 H), 3,43 - 3,74 (m, 2 H), 4,20 (d, J = 6,4 Hz, 1 H), 6,47 (d, J = 8,5 Hz, 2 H), 6,68 (br. s., 1

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H), 7,51 (d, J = 8,5 Hz, 2 H), 7,86 - 8,05 (m, 2 H), 8,31 (s, 1 H), 8,57 (s, 1 H).

Ejemplo 2

Ácido 3-[({4-[(ciclohexil{3-metil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



(1) 3-[metil(4-nitrobenzoil)amino]propanoato de etilo

Usando 3-(metilamino)propanoato de etilo (13,1 g) y de la misma manera que en el Ejemplo 1(1), se obtuvo el compuesto objeto del título (28,0 g, 100%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,26 (t, J = 7,1 Hz, 3 H), 2,51-2,78 (m, 2 H), 2,99-3,10 (m, 3H), 3,46-3,86 (m, 2 H), 4,03-4,28 (m, 2 H), 7,50-7,65 (m, 2 H), 8,28 (d, J = 8,7 Hz, 2 H).

(2) 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo

De la misma manera que en el Ejemplo 1(2), se obtuvo el compuesto objeto del título (26,6 g, 90%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,26 (t, J = 7,2 Hz, 3 H), 2,64 (t, J = 6,4 Hz, 2 H), 3,05 (s, 3 H), 3,74 (t, J = 7,0 Hz, 2

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H), 3,85 (br. s., 2 H), 4,14 (q, J = 7,2 Hz, 2 H), 6,59-6,72 (m, 2 H), 7,23-7,28 (m, 2 H).

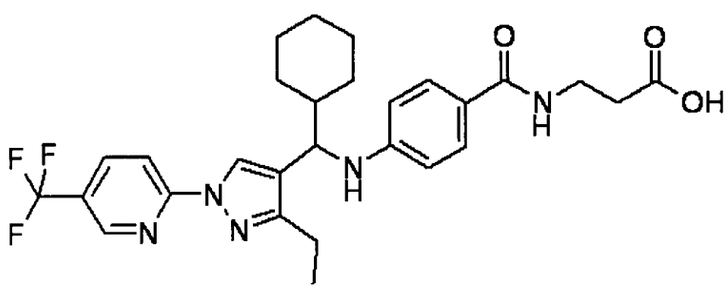
(3) Ácido 3-[({4-[(ciclohexil{3-metil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

Usando ciclohexil{3-metil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,75 g) sintetizado en el Ejemplo 1(6) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,80 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1 (7), se obtuvo el compuesto objeto del título (0,74 g, 65%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 2,23 (m, 11 H), 2,37 (s, 3 H), 2,62 - 2,78 (m, 2 H), 3,05 (s, 3 H), 3,58 - 3,84 (m, 2 H), 4,21 (d, J = 6,1 Hz, 1 H), 6,49 (d, J = 8,7 Hz, 2 H), 7,24 (d, J = 8,7 Hz, 2 H), 7,90 - 8,00 (m, 2 H), 8,32 (s, 1 H), 8,59 (s, 1 H).

Ejemplo 3

Ácido 3-[({4-[(ciclohexil{3-etil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico



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(1) 3-etil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo

Una mezcla de 3-oxopentanoato de metilo (2,6 g) y dimetilformamida dimetilacetal (2,8 mL) se agitó a 100 °C durante 12 h y se dejó enfriar. Etanol (50 mL) y monohidrato de hidrazina (1,1 mL) se añadieron a la mezcla de reacción y la mezcla se trató de la misma manera que en el Ejemplo 1(3) para dar un producto crudo de 3-etil-1H-pirazol-4-carboxilato de metilo. Esto se disolvió en dimetilformamida (30 ml), se añadieron carbonato de potasio (4,2 g) y 2-cloro-5-trifluorometilpiridina (3,6 g) y la mezcla se agitó a 100 °C durante 2 h. De la misma manera que en el Ejemplo 1(4), se obtuvo el compuesto objeto del título (4,7 g, 79%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,33 (t, J = 7,5 Hz, 3 H), 3,00 (q, J = 7,5 Hz, 2 H), 3,87 (s, 3 H), 7,99 - 8,18 (m, 2 H), 8,68 (s, 1 H), 9,00 (s, 1 H).

(2) 3-etil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído

El 3-etil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo (4,7 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (1,1 g, 26%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,35 (t, J = 7,6 Hz, 3 H), 3,00 (q, J = 7,6 Hz, 2 H), 7,98 - 8,23 (m, 2 H), 8,71 (s, 1 H), 9,04 (s, 1 H), 10,05 (s, 1 H).

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(3) ciclohexil{3-etil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol

El 3-etil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído (1,1 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (1,1 g, 79%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,80 - 2,21 (m, 14 H), 2,73 (q, J = 7,3 Hz, 2 H), 4,44 (dd, J = 7,2, 3,4 Hz, 1 H), 7,87 - 8,16 (m, 2 H), 8,43 (s, 1 H), 8,63 (s, 1 H).

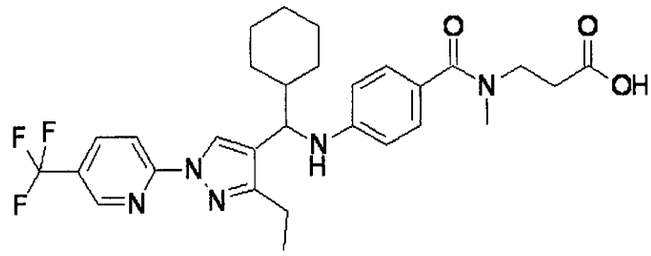
(4) ácido 3-[({4-[(ciclohexil{3-etil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

Usando ciclohexil{3-etil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,55 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,37 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1 (7), se obtuvo el compuesto objeto del título (0,32 g, 38%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 - 2,00 (m, 11 H), 1,32 (t, J = 7,5 Hz, 3 H), 2,38 - 2,58 (m, 2 H), 2,70 (q, J = 7,5 Hz, 2 H), 3,39 - 3,69 (m, 2 H), 4,22 (d, J = 6,0 Hz, 1 H), 6,47 (d, J = 8,5 Hz, 2 H), 6,68 (br. s., 1 H), 7,51 (d, J = 8,5 Hz, 2 H), 7,85 - 8,08 (m, 2 H), 8,30 (s, 1 H), 8,56 (s, 1 H).

Ejemplo 4

Ácido 3-[({4-[(ciclohexil{3-etil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

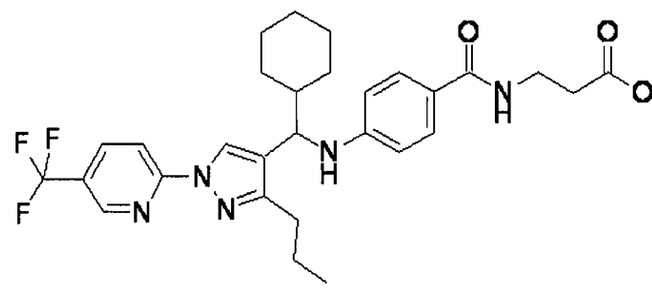


Usando ciclohexil{3-etil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,55 g) sintetizado en el Ejemplo 3(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,39 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,35 g, 41%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,19 - 2,06 (m, 11 H), 1,35 (t, J = 7,5 Hz, 3 H), 2,60 - 2,81 (m, 4 H), 3,05 (s, 3 H), 3,72 (d, J = 7,5 Hz, 1 H), 4,24 (d, J = 6,2 Hz, 1 H), 6,50 (d, J = 8,7 Hz, 2 H), 7,26 (d, J = 8,7 Hz, 2 H), 7,91 - 8,09 (m, 2 H), 8,31 (s, 1 H), 8,59 (s, 1 H).

Ejemplo 5

Ácido 3-[({4-[(ciclohexil{3-propil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico



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(1) 3-propil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo

Una mezcla de 3-oxohexanoato de metilo (2,1 g) y dimetilformamida dimetilacetal (2,1 mL) se agitó a 100 °C durante 12 h y la mezcla se dejó enfriar. A la mezcla de reacción se añadieron etanol (50 mL) y monohidrato de hidrazina (0,75 mL). De la misma manera que en el Ejemplo 1(3), se obtuvo un producto crudo de 3-propil-1H-pirazol-4-carboxilato de metilo. Esto se disolvió en dimetilformamida (20 ml), se añadieron carbonato de potasio (3,0 g) y 2-cloro-5-trifluorometilpiridina (2,7 g) y la mezcla se agitó a 100 °C durante 2 h. De la misma manera que en el Ejemplo 1(4), se obtuvo el compuesto objeto del título (3,3 g, 71%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 (t, J = 7,4 Hz, 3 H), 1,69 - 1,88 (m, 2 H), 2,93 (d, J = 7,7 Hz, 2 H), 3,87 (s, 3 H), 7,98 - 8,19 (m, 2 H), 8,69 (s, 1 H), 9,00 (s, 1 H).

(2) 3-propil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído

El 3-propil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo (3,3 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (1,1 g, 35%) en forma de un aceite amarillo.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 (t, J = 7,3 Hz, 3 H), 1,79 (m, 2 H), 2,94 (d, J = 7,7 Hz, 2 H), 8,00 - 8,23 (m, 2 H), 8,71 (s, 1 H), 9,04 (s, 1 H), 10,05 (s, 1 H).

(3) ciclohexil{3-propil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol

3-Propil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído (1,1 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (1,3 g, 95%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,80 - 2,21 (m, 16 H), 2,67 (q, J = 7,8 Hz, 2 H), 4,44 (dd, J = 7,5, 3,4 Hz, 1 H), 7,90 - 8,16 (m, 2 H), 8,43 (s, 1 H), 8,63 (s, 1 H).

(4) ácido 3-[({4-[(ciclohexil{3-propil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

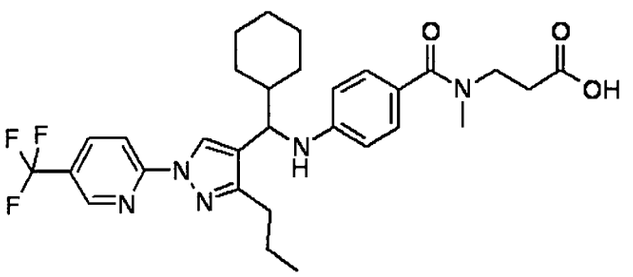
Usando ciclohexil{3-propil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,65 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,42 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,38 g, 39%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 (t, J = 7,4 Hz, 3 H), 1,07 - 2,04 (m, 13 H), 2,49 - 2,74 (m, 4 H), 3,52 - 3,72 (m, 2 H), 4,24 (d, J = 6,4 Hz, 1 H), 6,50 (d, J = 8,7 Hz, 2 H), 6,55 - 6,68 (m, 1 H), 7,53 (d, J = 8,7 Hz, 2 H), 7,86 - 8,08 (m, 2 H), 8,31 (s, 1 H), 8,57 (s, 1 H).

Ejemplo 6

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Ácido 3-[({4-[(ciclohexil{3-propil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



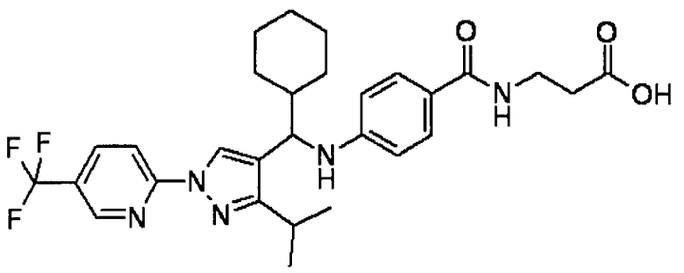
Usando ciclohexil{3-propil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,65 g) sintetizado en el Ejemplo 5(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,44 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,34 g, 34%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 (t, J = 7,2 Hz, 3 H), 1,08 - 2,13 (m, 13 H), 2,54 - 2,78 (m, 4 H), 3,05 (s, 3 H), 3,71 (t, J = 6,2 Hz, 1 H), 4,24 (d, J = 5,7 Hz, 1 H), 6,50 (d, J = 8,7 Hz, 2 H), 7,26 (d, J = 8,7 Hz, 2 H), 7,87 - 8,12 (m, 2 H), 8,31 (s, 1 H), 8,59 (s, 1 H).

Ejemplo 7

Ácido 3-[({4-[(ciclohexil{3-(1-metiletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

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(1) 3-(1-metiletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo

Usando 4-metil-3-oxopentanoato de metilo (2,9 g), dimetilformamida dimetilacetal (2,8 mL) y monohidrato de hidrazina (1,1 mL) y de la misma manera que en el Ejemplo 1(3), se obtuvo un producto crudo de 3-(1-metiletil)-1H-pirazol-4-carboxilato de metilo. Esto se disolvió en dimetilformamida (30 ml), se añadieron carbonato de potasio (4,2 g) y 2-cloro-5-trifluorometilpiridina (3,6 g) y la mezcla se agitó a 100 °C durante 2 h. De la misma manera que en el Ejemplo 1(4), se obtuvo el compuesto objeto del título (4,6 g, 73%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,36 (d, J = 6,8 Hz, 6 H), 3,60 (quint, J = 6,8 Hz, 1 H), 3,87 (s, 3 H), 7,99 - 8,99 (m, 4 H).

(2) 3-(1-metiletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído

El 3-(1-metiletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo (4,6 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (1,7 g, 40%) en forma de un sólido blanco.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,38 (d, J = 6,8 Hz, 6 H), 3,41 - 3,64 (m, 1 H), 8,01 - 8,28 (m, 2 H), 8,70 (s, 1 H), 9,04 (s, 1 H), 10,06 (s, 1 H).

(3)ciclohexil{3-(1-metiletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol

El 3-(1-metiletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído (1,7 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (1,5 g, 71%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,80 - 2,21 (m, 17 H), 3,01 (quint, J = 6,9 Hz, 1 H), 4,45 (dd, J = 7,5, 3,6 Hz, 1 H), 7,90 - 8,10 (m, 2 H), 8,43 (s, 1 H), 8,62 (s, 1 H).

Ácido (4)3-[({4-[(ciclohexil{3-(1-metiletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

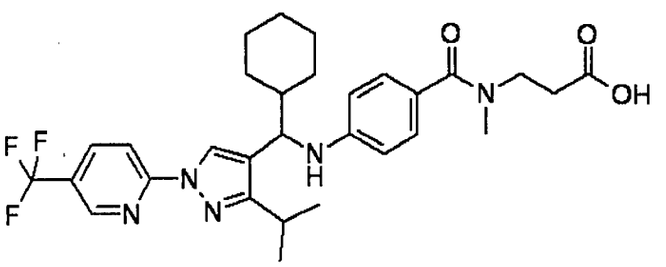
Usando ciclohexil{3-(1-metiletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,50 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,32 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,11 g, 14%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,20 - 2,06 (m, 11 H), 1,28 - 1,40 (m, 6 H), 2,64 (t, J = 4,5 Hz, 2 H), 2,91 - 3,17 (m, 1 H), 3,54 - 3,79 (m, 2 H), 4,29 (d, J = 6,2 Hz, 1 H), 6,43 - 6,65 (m, 3 H), 7,54 (d, J = 8,7 Hz, 2 H), 7,86 - 8,11 (m, 2 H), 8,30 (s, 1 H), 8,58 (s, 1 H).

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Ejemplo 8

Ácido 3-[({4-[(ciclohexil{3-(1-metiletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



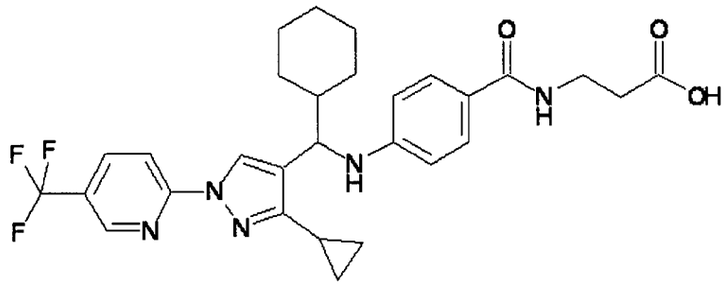
Usando ciclohexil{3-(1-metiletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,65 g) sintetizado en el Ejemplo 7(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,34 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,16 g, 21%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,20 - 2,05 (m, 11 H), 1,32 - 1,37 (m, 6 H), 2,59 - 2,79 (m, 2 H), 2,96 - 3,20 (m, 4 H), 3,73 (t, J = 7,5 Hz, 2 H), 4,28 (d, J = 6,0 Hz, 1 H), 6,52 (d, J = 8,7 Hz, 2 H), 7,26 (d, J = 8,7 Hz, 2 H), 7,88 - 8,11 (m, 2 H), 8,30 (s, 1 H), 8,59 (s, 1 H).

Ejemplo 9

Ácido 3-[({4-[(ciclohexil{3-ciclopropil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

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(1) 3-ciclopropil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo

Usando 3-ciclopropil-3-oxopropanoato de metilo (2,8 g), dimetilformamida dimetilacetal (2,8 mL) y monohidrato de hidrazina (1,1 mL) y de la misma manera que en el Ejemplo 1(3), se obtuvo un producto crudo de 3-ciclopropil-1H-pirazol-4-carboxilato de metilo. Esto se disolvió en dimetilformamida (30 ml), se añadieron carbonato de potasio (4,2 g) y 2-cloro-5-trifluorometilpiridina (3,6 g) y la mezcla se agitó a 100 °C durante 2 h. De la misma manera que en el Ejemplo 1(4), se obtuvo el compuesto objeto del título (4,8 g, 77%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,10 (m, 4 H), 2,55 - 2,70 (m, 1 H), 3,89 (s, 3 H), 8,00 - 8,03 (m, 2 H), 8,66 (s, 1 H), 8,96 (s, 1 H).

(2) 3-ciclopropil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído

El 3-ciclopropil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo (4,8 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (1,5 g, 36%) en forma de un sólido blanco.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,15 (m, 4 H), 2,50 - 2,70 (m, 1 H), 8,00 - 8,10 (m, 2 H), 8,69 (s, 1 H), 8,99 (s, 1 H), 10,10 (s, 1 H).

(3) ciclohexil{3-ciclopropil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol

El 3-ciclopropil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído (1,5 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (2,1 g, 99%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,80 - 2,10 (m, 16 H), 4,48 (dd, J = 7,3, 3,0 Hz, 1 H), 7,90 - 8,10 (m, 2 H), 8,40 (s, 1 H), 8,60 (s, 1 H).

(4) ácido 3-[({4-[(ciclohexil{3-ciclopropil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

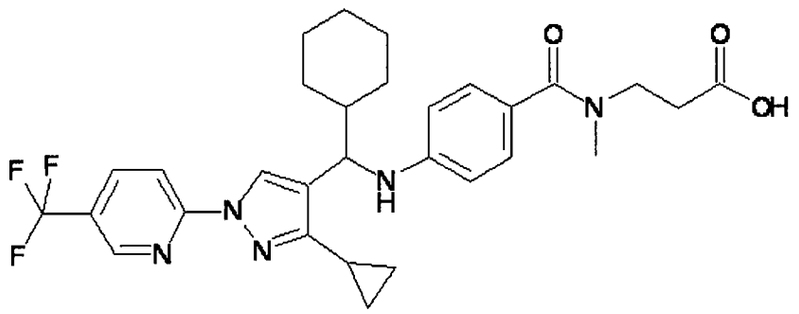
Usando ciclohexil{3-ciclopropil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,50 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,32 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,15 g, 21%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 - 2,07 (m, 16 H), 2,64 (t, J = 5,5 Hz, 2 H), 3,65 (q, J = 5,9 Hz, 2 H), 4,37 (d, J = 6,4 Hz, 1 H), 6,54 - 6,70 (m, 3 H), 7,53 (d, J = 8,3 Hz, 2 H), 7,93 (s, 2 H), 8,28 (s, 1 H), 8,56 (s, 1 H).

Ejemplo 10

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Ácido 3-[({4-[(ciclohexil{3-ciclopropil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



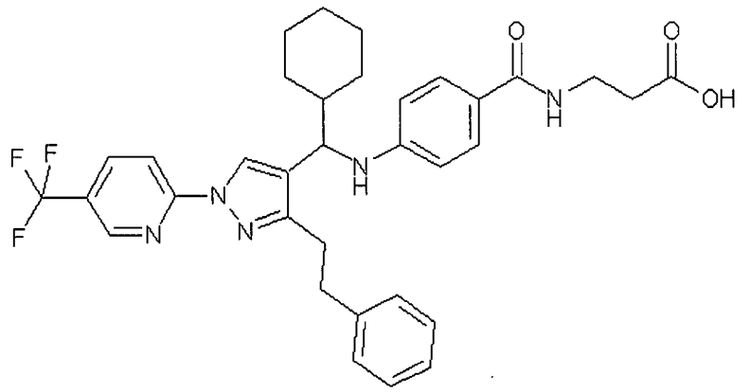
Usando ciclohexil{3-ciclopropil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,50 g) sintetizado en el Ejemplo 9(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,34 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,19 g, 25%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 2,09 (m, 16 H), 2,71 (t, J = 6,2 Hz, 2 H), 3,07 (s, 3 H), 3,71 (t, J = 6,4 Hz, 2 H), 4,36 (d, J = 6,4 Hz, 1 H), 6,54 (d, J = 8,7 Hz, 2 H), 7,26 (d, J = 8,7 Hz, 2 H), 7,94 (s, 2 H), 8,28 (s, 1 H), 8,57 (s, 1 H).

Ejemplo 11

Ácido 3-[({4-[(ciclohexil{3-(2-feniletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

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(1) 3-(2-feniletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de etilo

Usando 3-oxo-5-fenilpentanoato de etilo (5,8 g), dimetilformamida dimetilacetal (3,6 mL) y monohidrato de hidrazina (1,3 mL) y de la misma manera que en el Ejemplo 1(3), se obtuvo un producto crudo de 3-(2-feniletil)-1H-pirazol-4-carboxilato de etilo. Esto se disolvió en dimetilformamida (30 ml), se añadieron carbonato de potasio (5,5 g) y 2-cloro-5-trifluorometilpiridina (4,8 g) y la mezcla se agitó a 100 °C durante la noche. De la misma manera que en el Ejemplo 1(4), se obtuvo el compuesto objeto del título (5,2 g, 50%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,39 (t, J = 7,2 Hz, 3 H), 3,00 - 3,15 (m, 2 H), 3,22 - 3,39 (m, 2 H), 4,34 (q, J = 7,2 Hz, 2 H), 7,15 - 7,38 (m, 10 H), 7,99 - 8,17 (m, 2 H), 8,69 (s, 1 H), 9,01 (s, 1 H).

(2) 3-(2-feniletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído

El 3-(2-feniletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de etilo (5,2 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo

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1(5) para dar el compuesto objeto del título (3,0 g, 65%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,98 - 3,17 (m, 2 H), 3,22 - 3,41 (m, 2 H), 7,11 - 7,47 (m, 5 H), 7,99 - 8,22 (m, 2 H), 8,71 (s, 1 H), 9,04 (s, 1 H), 9,99 (s, 1 H).

(3) ciclohexil{3-(2-feniletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol

El 3-(2-feniletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído (1,5 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (1,7 g, 95%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,83 - 2,02 (m, 12 H), 2,92 - 3,23 (m, 4 H), 4,28 (dd, J = 7,3, 2,7 Hz, 1 H), 7,15 - 7,40 (m, 5 H), 7,93 - 8,13 (m, 2 H), 8,42 (s, 1 H), 8,64 (s, 1 H).

(4) ácido 3-[({4-[(ciclohexil{3-(2-feniletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

Usando ciclohexil{3-(2-feniletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,50 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,28 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,20 g, 28%) en forma de un sólido blanco.

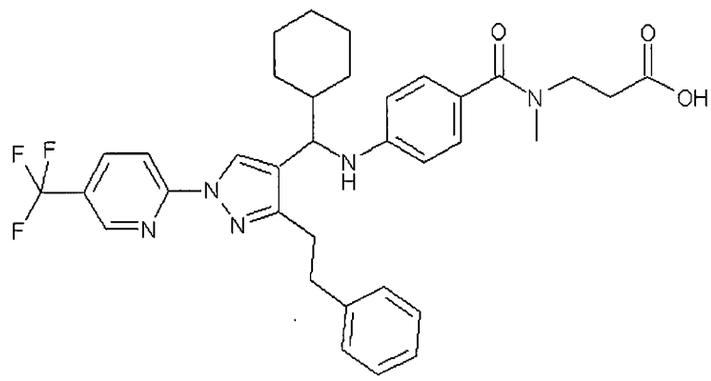
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 - 1,97 (m, 11 H), 2,45 - 2,64 (m, 2 H), 2,87 - 3,18 (m, 4 H), 3,49 - 3,67 (m, 2 H), 4,16 (d, J = 6,0 Hz, 1 H), 6,41 (d, J = 8,7 Hz, 2 H), 6,61

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(br. s., 1 H), 7,15 - 7,34 (m, 5 H), 7,49 (d, J = 8,7 Hz, 2 H), 7,87 - 8,10 (m, 2 H), 8,31 (s, 1 H), 8,57 (s, 1 H).

Ejemplo 12

Ácido 3-[({4-[(ciclohexil{3-(2-feniletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



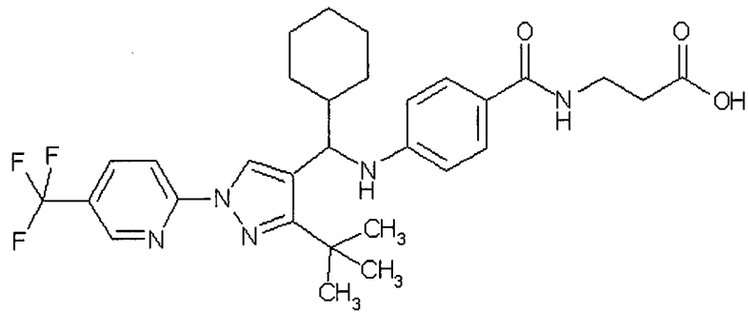
Usando ciclohexil{3-(2-feniletil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,50 g) sintetizado en el Ejemplo 11(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,35 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,30 g, 41%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 2,01 (m, 11 H), 2,59 - 2,74 (m, 2 H), 2,89 - 3,20 (m, 7 H), 3,71 (d, J = 6,0 Hz, 2 H), 4,18 (d, J = 6,0 Hz, 1 H), 6,43 (d, J = 8,7 Hz, 2 H), 7,16 - 7,37 (m, 5 H), 7,90 - 8,13 (m, 2 H), 8,32 (s, 1 H), 8,60 (s, 1 H).

Ejemplo 13

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Ácido 3-{[(4-{[{3-ter-butil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico



(1) 3-ter-butil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo

Usando 4,4-dimetil-3-oxopentanoato de etilo (3,4 g), dimetilformamida dimetilacetal (2,8 mL) y monohidrato de hidrazina (1,1 mL) y de la misma manera que en el Ejemplo 1(3), se obtuvo un producto crudo de 3-ter-butil-1H-pirazol-4-carboxilato de metilo. Esto se disolvió en dimetilformamida (15 ml), se añadieron carbonato de potasio (1,2 g) y 2-cloro-5-trifluorometilpiridina (1,7 g) y la mezcla se agitó a temperatura ambiente durante la noche. De la misma manera que en el Ejemplo 1(4), se obtuvo el compuesto objeto del título (2,8 g, 43%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,38 (t, J = 7,2 Hz, 3 H), 1,49 (s, 9 H), 4,32 (q, J = 7,2 Hz, 2 H), 7,98 - 8,21 (m, 2 H), 8,68 (d, J = 1,1 Hz, 1 H), 9,03 (s, 1 H).

(2) 3-ter-butil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído

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El 3-ter-butil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo (2,8 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (1,7 g, 93%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,49 (s, 9 H), 7,98 - 8,21 (m, 2 H), 8,68 (d, J = 1,1 Hz, 1 H), 9,09 (s, 1 H), 10,11 (s, 1 H).

(3) ciclohexil{3-ter-butil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol

El 3-ter-butil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído (1,7 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (1,1 g, 49%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,79 - 2,20 (m, 12 H), 1,43 (s, 9 H), 4,65 (d, J = 9,0 Hz, 1 H), 7,91 - 8,15 (m, 2 H), 8,52 (s, 1 H), 8,62 (s, 1 H).

(4) ácido 3-{[(4-{[{3-ter-butil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico

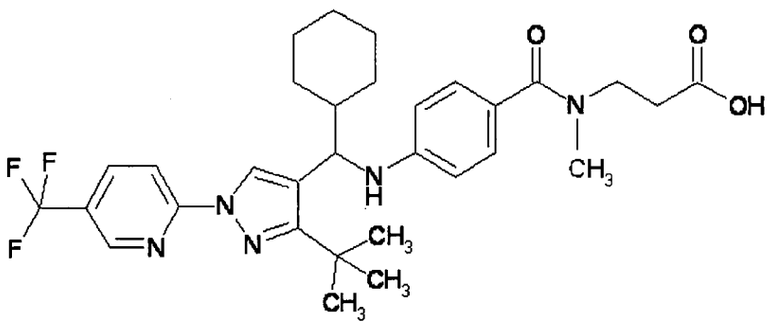
Usando ciclohexil{3-ter-butil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,53 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,32 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,12 g, 15%) en forma de un sólido blanco.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 2,00 (m, 11 H), 1,27 (s, 9 H), 2,57 - 2,61 (m, 2 H), 3,17 - 3,59 (m, 2 H), 4,44 (br. s., 1 H), 6,31 - 6,51 (m, 2 H), 7,33 - 7,47 (m, 1 H), 7,49 - 7,62 (m, 2 H), 7,74 - 8,07 (m, 2 H), 8,32 - 8,57 (m, 2 H).

Ejemplo 14

Ácido 3-{[(4-{[{3-ter-butil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico



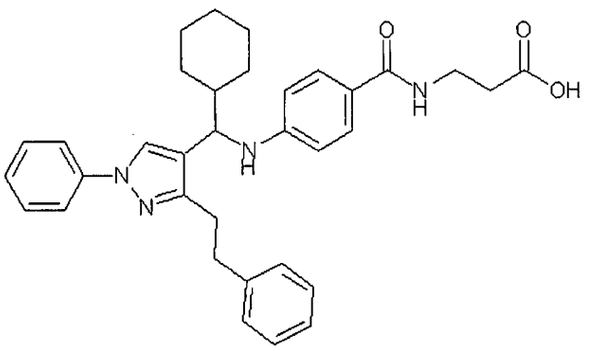

Usando ciclohexil{3-ter-butil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,52 g) sintetizado en el Ejemplo 13(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,34 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,13 g, 16%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 2,00 (m, 11 H), 1,42 (s, 9 H), 2,61 - 2,81 (m, 2 H), 3,08 (s, 3 H), 3,72 (t, J = 6,4 Hz, 2 H), 4,57 (d, J = 6,1 Hz, 1 H), 6,54 (d, J = 8,7 Hz, 2 H), 7,26 (d, J = 8,7 Hz, 2 H), 7,89 - 8,13 (m, 2 H), 8,40 (s, 1 H), 8,59 (s, 1 H).

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Ejemplo 15

Ácido 3-({[4-({ciclohexil[1-fenil-3-(2-feniletil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico



(1) 1-fenil-3-(2-feniletil)-1H-pirazol-4-carboxilato de etilo

Una mezcla de 3-oxo-5-fenilpentanoato de etilo (5,8 g) y dimetilformamida dimetilacetal (3,6 mL) se agitó a 100 °C durante la noche y la mezcla se dejó enfriar hasta temperatura ambiente. A la mezcla de reacción se añadieron etanol (30 mL) y fenilhidrazina (2,9 g) y la mezcla luego se agitó a 100 °C durante 8 h. Después de enfriar, el etanol se evaporó a presión reducida. Se añadió agua al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:10, relación en volumen) para dar el compuesto objeto del título (7,1 g, 84%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,40 (t, J = 7,2 Hz, 3 H), 2,87 (dd, J = 9,0, 6,6 Hz, 2 H), 3,15 - 3,32 (m, 2 H), 4,36 (q, J

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= 7,2 Hz, 2 H), 6,92 - 7,53 (m, J = 7,5, 3,8, 3,8, 3,5 Hz, 10 H), 8,05 (s, 1 H).

(2) 1-fenil-3-(2-feniletil)-1H-pirazol-4-carbaldehído

El 1-fenil-3-(2-feniletil)-1H-pirazol-4-carboxilato de etilo (7,1 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (4,6 g, 75%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,87 (t, J = 7,8 Hz, 2 H), 3,23 (t, J = 7,6 Hz, 2 H), 6,84 - 7,58 (m, 10 H), 8,07 (s, 1 H), 9,93 (s, 1 H).

(3) ciclohexil[1-fenil-3-(2-feniletil)-1H-pirazol-4-il]metanol

El 1-fenil-3-(2-feniletil)-1H-pirazol-4-carbaldehído (2,6 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (2,9 g, 85%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,75 - 2,19 (m, 12 H), 2,46 - 3,17 (m, 4 H), 4,16 (dd, J = 8,3, 2,7 Hz, 1 H), 6,83 - 7,54 (m, 10 H), 7,58 (s, 1 H).

(4) ácido 3-({[4-({ciclohexil[1-fenil-3-(2-feniletil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico

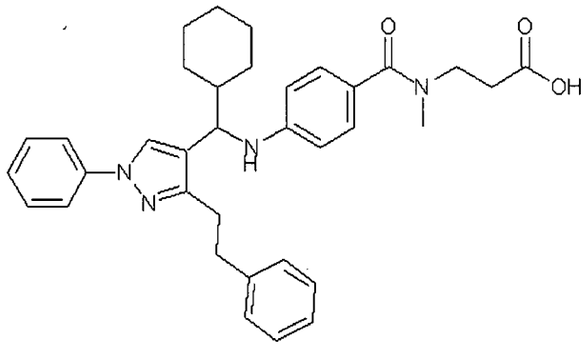
Usando ciclohexil[1-fenil-3-(2-feniletil)-1H-pirazol-4-il]metanol (0,50 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,33 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,31 g, 41%) en forma de un sólido blanco.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 2,03 (m, 11 H), 2,40 - 2,56 (m, 2 H), 2,67 (t, J = 5,7 Hz, 2 H), 2,91 - 3,07 (m, 2 H), 3,68 (q, J = 5,9 Hz, 2 H), 4,20 (d, J = 7,0 Hz, 1 H), 6,52 - 6,58 (m, J = 8,7 Hz, 3 H), 6,82 (d, J = 8,6 Hz, 2 H), 7,12 - 7,22 (m, 4 H), 7,35 - 7,65 (m, 11 H).

Ejemplo 16

Ácido 3-[{[4-({ciclohexil[1-fenil-3-(2-feniletil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



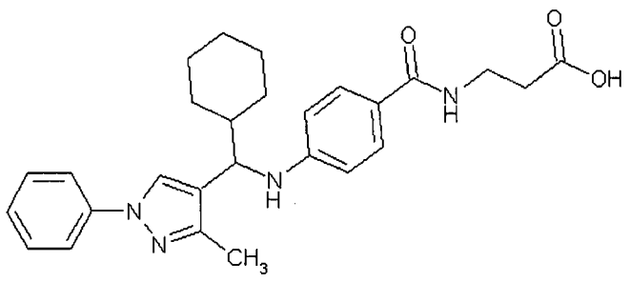

Usando ciclohexil[1-fenil-3-(2-feniletil)-1H-pirazol-4-il]metanol (0,50 g) sintetizado en el Ejemplo 15(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,35 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,37 g, 47%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 2,08 (m, 11 H), 2,44 - 2,59 (m, 2 H), 2,73 (d, J = 6,0 Hz, 2 H), 2,91 - 3,05 (m, 2 H), 3,09 (s, 3 H), 3,73 (t, J = 6,4 Hz, 2 H), 4,19 (d, J = 6,8 Hz, 1 H), 6,53 (d, J = 8,7 Hz, 2 H), 6,79 - 6,88 (m, 2 H), 7,12 - 7,58 (m, 11 H).

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Ejemplo 17

Ácido 3-{[(4-{[ciclohexil(3-metil-1-fenil-1H-pirazol-4-il)metil]amino}fenil)carbonil]amino}propanoico



(1) 3-metil-1-fenil-1H-pirazol-4-carboxilato de metilo

El 3-metil-1H-pirazol-4-carboxilato de metilo (14,4 g) sintetizado en el Ejemplo 1, (3) se disolvió en dimetilacetamida (200 mL), se añadieron ácido fenilborónico (25,0 g), acetato de cobre (36,4 g) y piridina (32 mL) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite, se añadió ácido clorhídrico 1 N (100 mL) al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 10:1, relación en volumen) para dar el compuesto objeto del título (11,4 g, 53%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,56 (s, 3H), 3,86 (s, 3H), 7,26-7,70 (m, 5H), 8,34 (s, 1H).

(2) 3-metil-1-fenil-1H-pirazol-4-carbaldehído

1003

El 3-metil-1-fenil-1H-pirazol-4-carboxilato de metilo (11,4 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (3,8 g, 39%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,59 (s, 3H), 7,27-7,72 (m, 5H), 8,34 (s, 1H), 10,00 (s, 1H).

(3) ciclohexil(3-metil-1-fenil-1H-pirazol-4-il)metanol

El 3-Metil-1-fenil-1H-pirazol-4-carbaldehído (3,8 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (4,4 g, 79%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,80-2,20 (m, 11H), 2,34 (s, 3H), 3,61 (br s, 1H), 4,44 (d, J = 7,2 Hz, 1H), 7,20-7,80 (m, 6H).

(4) ácido 3-{[(4-{[ciclohexil(3-metil-1-fenil-1H-pirazol-4-il)metil]amino}fenil)carbonil]amino}propanoico

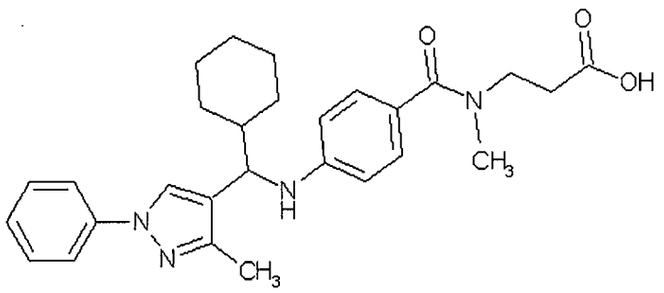
Usando ciclohexil(3-metil-1-fenil-1H-pirazol-4-il)metanol (0,14 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,15 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,05 g, 31%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,04 - 2,21 (m, 12 H), 2,36 (s, 3 H), 2,65 (br. s., 2 H), 3,67 (br. s., 2 H), 4,20 (d, J = 6,0 Hz, 1 H), 6,49 (d, J = 6,0 Hz, 2 H), 6,55 - 6,71 (m, 1 H), 7,14 - 7,74 (m, 8 H).

Ejemplo 18

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Ácido 3-{[(4-{[ciclohexil(3-metil-1-fenil-1H-pirazol-4-il)metil]amino}fenil)carbonil](metil)amino}propanoico



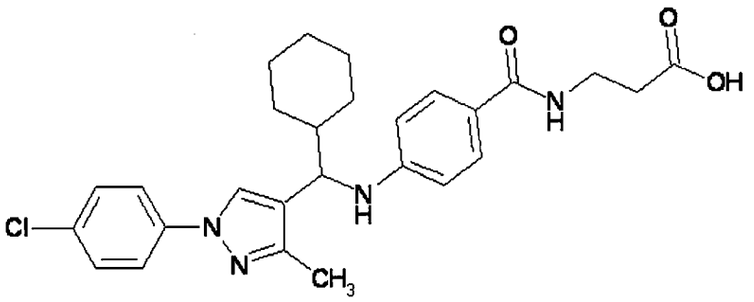
Usando ciclohexil(3-metil-1-fenil-1H-pirazol-4-il)metanol (0,14 g) sintetizado en el Ejemplo 17(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,15 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,04 g, 23%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,87 - 2,10 (m, 12 H), 2,25 (s, 3 H), 2,47 (t, J = 7,4 Hz, 2 H), 2,89 (s, 3 H), 3,51 (t, J = 7,4 Hz, 2 H), 4,16 (t, J = 7,6 Hz, 1 H), 6,22 (d, J = 8,0 Hz, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 7,10 (d, J = 8,7 Hz, 2 H), 7,22 (t, J = 7,2 Hz, 1 H), 7,43 (t, J = 8,0 Hz, 1 H).

Ejemplo 19

Ácido 3-({[4-({[1-(4-clorofenil)-3-metil-1H-pirazol-4-il](ciclohexil)metil}amino)fenil]carbonil}amino)propanoico

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(1) 1-(4-clorofenil)-3-metil-1H-pirazol-4-carboxilato de metilo

Usando 3-metil-1H-pirazol-4-carboxilato de metilo (6,25 g) sintetizado en el Ejemplo 1(3), ácido 4-clorofenilborónico (13,9 g), acetato de cobre (16,3 g) y piridina (14,4 mL) y de la misma manera que en el Ejemplo 17(1), se obtuvo el compuesto objeto del título (6,9 g, 62%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 2,54 (s, 3 H), 3,85 (s, 3 H), 7,43 (d, J = 8,7 Hz, 2 H), 7,62 (d, J = 8,7 Hz, 2 H), 8,31 (s, 1 H).

(2) 1-(4-clorofenil)-3-metil-1H-pirazol-4-carbaldehído

El 1-(4-clorofenil)-3-metil-1H-pirazol-4-carboxilato de metilo (6,9 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (4,1 g, 68%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,58 (s, 3 H), 7,46 (d, J = 9,0 Hz, 2 H), 7,64 (d, J = 9,0 Hz, 2 H), 8,31 (s, 1 H), 10,00 (s, 1 H).

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(3) [1-(4-clorofenil)-3-metil-1H-pirazol-4-il](ciclohexil)metanol

El 1-(4-clorofenil)-3-metil-1H-pirazol-4-carbaldehído (4,2 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (4,9 g, 85%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,88 - 2,00 (m, 11 H), 2,32 (s, 3 H), 3,59 (br. s., 1 H), 4,43 (d, J = 7,2 Hz, 1 H), 7,38 (d, J = 9,0 Hz, 2 H), 7,58 (d, J = 9,0 Hz, 2 H), 7,76 (s, 1 H).

(4) ácido 3-({[4-({[1-(4-clorofenil)-3-metil-1H-pirazol-4-il](ciclohexil)metil}amino)fenil]carbonil}amino)propanoico

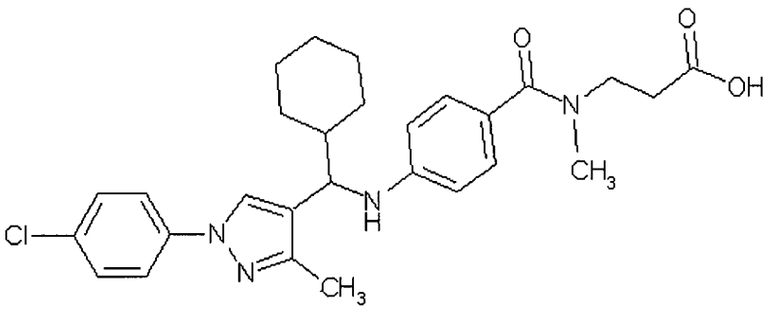
Usando [1-(4-clorofenil)-3-metil-1H-pirazol-4-il](ciclohexil)metanol (0,46 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,35 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,42 g, 57%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,86 - 2,09 (m, 12 H), 2,24 (s, 3 H), 2,41 (t, J = 7,1 Hz, 2 H), 3,28 - 3,44 (m, 2 H), 4,20 (t, J = 7,7 Hz, 1 H), 6,33 (d, J = 7,9 Hz, 1 H), 6,58 (d, J = 8,9 Hz, 2 H), 7,39 - 7,60 (m, 4 H), 7,73 (d, J = 9,0 Hz, 2 H), 7,92 - 8,09 (m, 1 H), 8,29 (s, 1 H).

Ejemplo 20

Ácido 3-[{[4-({[1-(4-clorofenil)-3-metil-1H-pirazol-4-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoico

1007

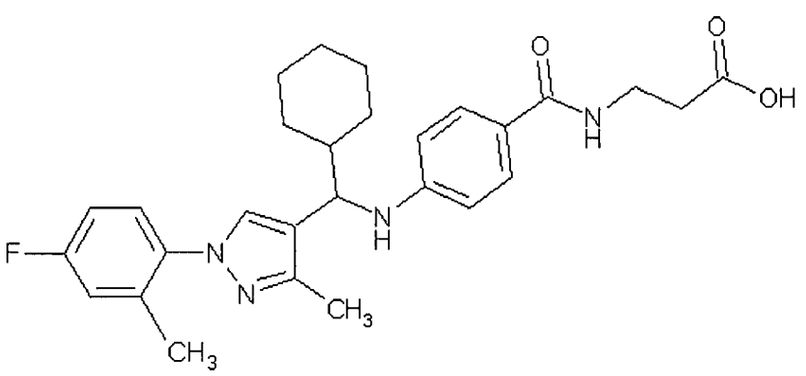


Usando [1-(4-clorofenil)-3-metil-1H-pirazol-4-il](ciclohexil)metanol (0,46 g) sintetizado en el Ejemplo 19(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,25 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,41 g, 57%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,75 - 2,07 (m, 12 H), 2,23 (s, 5 H), 2,85 (br. s., 3 H), 3,39 - 3,57 (m, 2 H), 4,13 (br. s., 1 H), 6,20 (d, J = 7,0 Hz, 1 H), 6,56 (d, J = 8,5 Hz, 2 H), 7,09 (d, J = 8,5 Hz, 2 H), 7,46 (d, J = 8,7 Hz, 2 H), 7,71 (d, J = 8,7 Hz, 2 H), 8,28 (s, 1 H).

Ejemplo 21

Ácido 3-({[4-({[1-(4-fluoro-2-metilfenil)-3-metil-1H-pirazol-4-il](ciclohexil)metil}amino)fenil]carbonil}amino)propanoico



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(1) 1-(4-fluoro-2-metilfenil)-3-metil-1H-pirazol-4-carboxilato de metilo

Usando 3-metil-1H-pirazol-4-carboxilato de metilo (6,25 g) sintetizado en el Ejemplo 1(3) y ácido 4-fluoro-2-metilfenilborónico (13,9 g) y de la misma manera que en el Ejemplo 17(1), se obtuvo el compuesto objeto del título (7,5 g, 68%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,26 (s, 3 H), 2,54 (s, 3 H), 3,85 (s, 3 H), 6,80 - 7,35 (m, 3 H), 7,97 (s, 1 H).

(2) 1-(4-fluoro-2-metilfenil)-3-metil-1H-pirazol-4-carbaldehído

El 1-(4-fluoro-2-metilfenil)-3-metil-1H-pirazol-4-carboxilato de metilo (7,5 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (4,3 g, 83%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,24 (s, 3 H), 2,57 (s, 3 H), 6,90 - 7,39 (m, 3 H), 7,99 (s, 1 H), 10,00 (s, 1 H).

(3) ciclohexil[1-(4-fluoro-2-metilfenil)-3-metil-1H-pirazol-4-il]metanol

El 1-(4-Fluoro-2-metilfenil)-3-metil-1H-pirazol-4-carbaldehído (4,3 g) sintetizada con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (6,1 g, 98%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,88 - 2,00 (m, 11 H), 2,22 (s, 3 H), 2,32 (s, 3 H), 4,44 (dd, J = 7,3, 3,3 Hz, 1 H), 6,91 - 7,30 (m, 3 H), 7,41 (s, 1 H).

1009

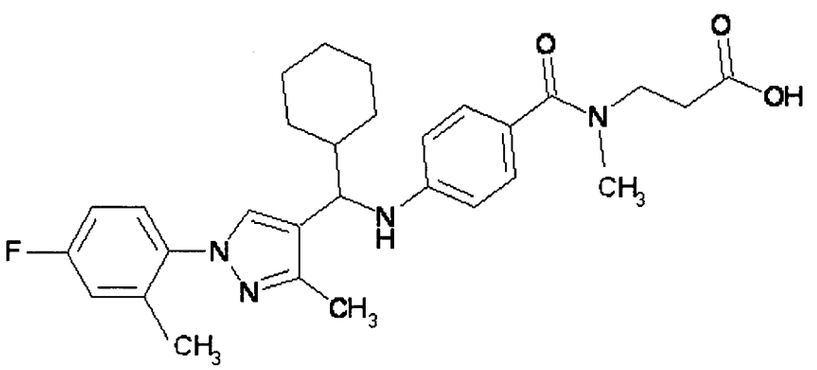
(4) ácido 3-({[4-({[1-(4-fluoro-2-metilfenil)-3-metil-1H-pirazol-4-
il](ciclohexil)metil}amino)fenil]carbonil}amino)propanoico

Usando ciclohexil[1-(4-fluoro-2-metilfenil)-3-metil-1H-pirazol-4-il]metanol (0,50 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,55 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,52 g, 70%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,87 - 2,00 (m, 12 H), 2,12 (s, 3 H), 2,21 (s, 3 H), 2,34 (t, J = 7,1 Hz, 2 H), 3,22 - 3,45 (m, 2 H), 4,21 (t, J = 7,7 Hz, 1 H), 6,31 (d, J = 8,1 Hz, 1 H), 6,59 (d, J = 8,9 Hz, 2 H), 7,10 - 7,31 (m, 3 H), 7,51 (d, J = 8,7 Hz, 2 H), 7,76 (s, 1 H), 8,11 (s, 1 H).

Ejemplo 22

Ácido 3-[{[4-({[1-(4-fluoro-2-metilfenil)-3-metil-1H-pirazol-4-
il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoico




Usando ciclohexil[1-(4-fluoro-2-metilfenil)-3-metil-1H-pirazol-4-il]metanol (0,50 g) sintetizado en el Ejemplo 21(3)

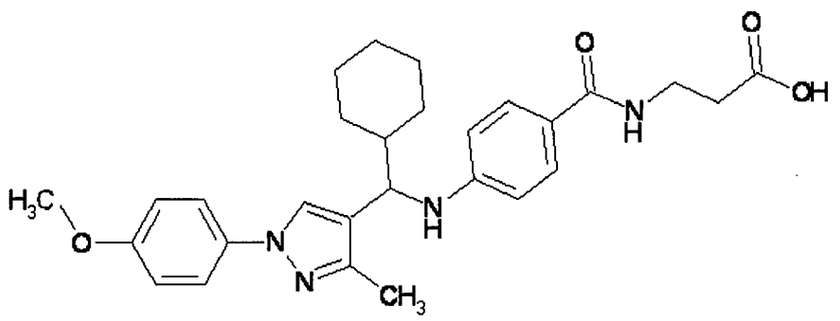
1010

y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,39 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,48 g, 60%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,87 - 1,84 (m, 12 H), 2,10 (s, 3 H), 2,22 (s, 3 H), 2,48 - 2,50 (m, 2 H), 2,91 (s, 3 H), 3,52 (m, 2 H), 4,16 (d, J = 9,0 Hz, 1 H), 6,59 (d, J = 8,7 Hz, 2 H), 7,00 - 7,32 (m, 6 H), 7,75 (s, 1 H).

Ejemplo 23

Ácido 3-({[4-({ciclohexil[1-(4-metoxifenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico




(1) 1-(4-metoxifenil)-3-metil-1H-pirazol-4-carboxilato de metilo

Usando 3-metil-1H-pirazol-4-carboxilato de metilo (5,7 g) sintetizado en el Ejemplo 1(3) y ácido 4-metoxifenilborónico (12,4 g) y de la misma manera que en el Ejemplo 17(1), se obtuvo el compuesto objeto del título (6,5 g, 65%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,55 (s, 3 H), 3,83 (s, 3 H), 3,85 (s, 3 H), 6,97 (d, J = 9,0 Hz, 2 H), 7,57 (d, J = 9,0 Hz, 2 H), 8,23 (s, 1 H).

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(2) 1-(4-metoxifenil)-3-metil-1H-pirazol-4-carbaldehído

El 1-(4-metoxifenil)-3-metil-1H-pirazol-4-carboxilato de metilo (6,6 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (4,1 g, 78%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,58 (s, 3 H), 3,86 (s, 3 H), 6,99 (d, J = 9,0 Hz, 2 H), 7,59 (d, J = 8,9 Hz, 2 H), 8,24 (s, 1 H), 9,98 (s, 1 H).

(3) ciclohexil[1-(4-metoxifenil)-3-metil-1H-pirazol-4-il]metanol

El 1-(4-metoxifenil)-3-metil-1H-pirazol-4-carbaldehído (4,3 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (7,1 g, 98%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,88 - 1,97 (m, 11 H), 2,33 (s, 3 H), 3,59 (br. s., 1 H), 3,83 (s, 3 H), 4,43 (dd, J = 7,3, 3,0 Hz, 1 H), 6,94 (d, J = 9,0 Hz, 2 H), 7,53 (d, J = 9,2 Hz, 2 H), 7,70 (s, 1 H).

(4) Ácido 3-({[4-({ciclohexil[1-(4-metoxifenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico

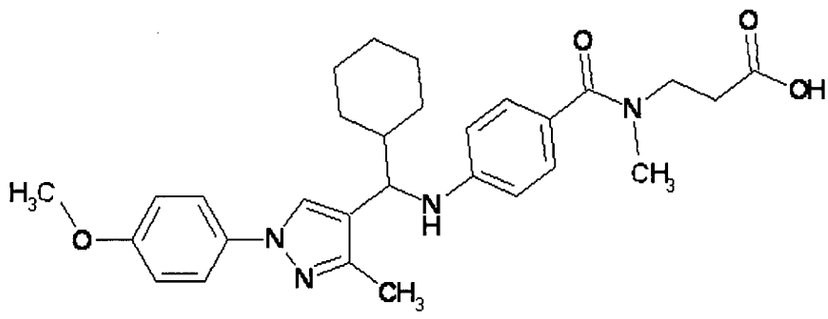
Usando ciclohexil[1-(4-metoxifenil)-3-metil-1H-pirazol-4-il]metanol (0,68 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,55 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,44 g, 39%) en forma de un sólido blanco.

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$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,89 - 2,08 (m, 12 H), 2,22 (s, 3 H), 2,34 - 2,45 (m, 2 H), 3,44-3,60 (m, 2H), 3,76 (s, 3 H), 4,07 - 4,27 (m, 1 H), 6,30 (d, J = 9,0 Hz, 1 H), 6,58 (d, J = 8,9 Hz, 2 H), 6,99 (d, J = 9,2 Hz, 2 H), 7,51 (d, J = 8,9 Hz, 2 H), 7,60 (d, J = 9,2 Hz, 2 H), 8,03 (br. s., 1 H), 8,14 (s, 1 H).

Ejemplo 24

Ácido 3-[{[4-({ciclohexil[1-(4-metoxifenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico




Usando ciclohexil[1-(4-metoxifenil)-3-metil-1H-pirazol-4-il]metanol (0,68 g) sintetizado en el Ejemplo 23(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,42 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,28 g, 24%) en forma de un sólido blanco.

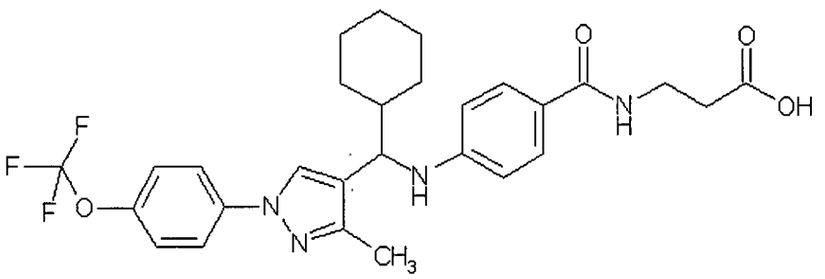
$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,87 - 2,10 (m, 12 H), 2,23 (s, 3 H), 2,45-2,50 (m, 2H), 2,90 (s, 3 H), 3,44 - 3,60 (m, 2 H), 3,77 (s, 3 H), 4,13-4,15 (m, 1 H), 6,21 (d, J = 7,7 Hz, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 6,99 (d, J = 9,0 Hz, 2 H),

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7,10 (d, J = 8,7 Hz, 2 H), 7,60 (d, J = 9,0 Hz, 2 H), 8,14 (s, 1 H).

Ejemplo 25

Ácido 3-[({4-[(ciclohexil{3-metil-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico



(1) 3-metil-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carboxilato de metilo

Usando 3-metil-1H-pirazol-4-carboxilato de metilo (6,8 g) sintetizado en el Ejemplo 1(3) y ácido 4-trifluorometoxifenilborónico (20,0 g) y de la misma manera que en el Ejemplo 17(1), se obtuvo el compuesto objeto del título (3,9 g, 27%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,55 (s, 3 H), 3,86 (s, 3 H), 7,32 (d, J = 9,2 Hz, 2 H), 7,71 (d, J = 9,2 Hz, 2 H), 8,32 (s, 1 H).

(2) 3-metil-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carbaldehído

El 3-metil-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carboxilato de metilo (3,9 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el

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compuesto objeto del título (2,3 g, 66%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,59 (s, 3 H), 7,36 (d, J = 9,0 Hz, 2 H), 7,73 (d, J = 9,0 Hz, 2 H), 8,32 (s, 1 H), 10,01 (s, 1 H).

(3) ciclohexil{3-metil-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metanol

El 3-Metil-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carbaldehído (2,6 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (2,2 g, 72%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,89 - 1,91 (m, 11 H), 2,33 (s, 3 H), 4,44 (dd, J = 7,2, 3,0 Hz, 1 H), 7,26 (d, J = 9,2 Hz, 2 H), 7,66 (d, J = 9,2 Hz, 2 H), 7,77 (s, 1 H).

(4) ácido 3-[({4-[(ciclohexil{3-metil-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

Usando ciclohexil{3-metil-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metanol (0,59 g) sintetizada con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,55 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,50 g, 55%) en forma de un sólido blanco.

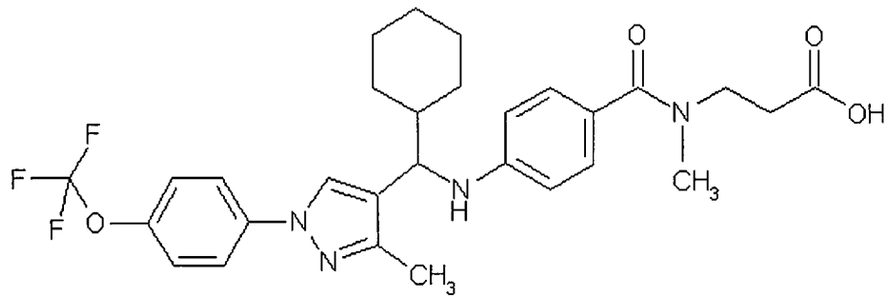
$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,85 - 2,11 (m, 11 H), 2,24 (s, 3 H), 2,39 (t, J = 7,2 Hz, 2 H), 3,30 - 3,43 (m, 2 H), 4,20 (t, J = 7,6 Hz, 1 H), 6,34 (d, J = 7,6 Hz, 1 H), 6,58

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(d, J = 8,3 Hz, 2 H), 7,34 - 7,61 (m, 4 H), 7,82 (d, J = 9,1 Hz, 2 H), 8,02 (br. s., 1H).

Ejemplo 26

Ácido 3-[({4-[(ciclohexil{3-metil-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



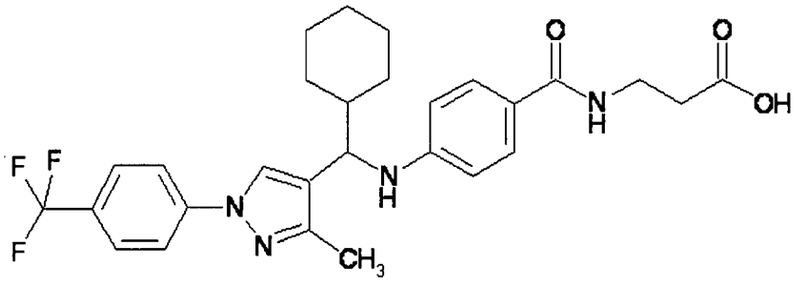
Usando ciclohexil{3-metil-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metanol (0,97 g) sintetizado en el Ejemplo 25(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,63 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (1,3 g, 63%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,89 - 2,06 (m, 11 H), 2,24 (s, 3 H), 2,40 (t, J = 7,0 Hz, 2 H), 3,28 - 3,45 (m, 5 H), 4,20 (t, J = 7,8 Hz, 1 H), 6,34 (d, J = 7,6 Hz, 1 H), 6,58 (d, J = 9,1 Hz, 2 H), 7,35 - 7,57 (m, 4 H), 7,82 (d, J = 9,1 Hz, 2 H), 8,01 (br s, 1 H).

Ejemplo 27

Ácido 3-[({4-[(ciclohexil{3-metil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

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(1) 3-metil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-carboxilato de metilo

Usando un producto crudo de 3-metil-1H-pirazol-4-carboxilato de metilo (8,9 g) sintetizado en el Ejemplo 1(3) y ácido 4-trifluorometilfenilborónico (13,3 g) y de la misma manera que en el Ejemplo 17(1), se obtuvo el compuesto objeto del título (2,0 g, 11%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,56 (s, 3 H), 3,87 (s, 3 H), 7,72 (d, J = 9,2 Hz, 2 H), 7,82 (d, J = 9,2 Hz, 2 H), 8,41 (s, 1 H).

(2) 3-metil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-carbaldehído

El 3-metil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-carboxilato de metilo (2,0 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (0,6 g, 30%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,56 (s, 3 H), 7,72 (d, J = 9,0 Hz, 2 H), 7,82 (d, J = 9,0 Hz, 2 H), 8,40 (s, 1 H), 9,98 (s, 1 H).

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(3) ciclohexil{3-metil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-il}metanol

El 3-metil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-carbaldehído (0,6 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (0,7 g, 93%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 1,98 (m, 11 H), 2,34 (s, 3 H), 3,53 - 3,69 (m, 1 H), 4,46 (d, J = 7,0 Hz, 1 H), 7,67 (d, J = 9,0 Hz, 2 H), 7,77 (d, J = 9,0 Hz, 2 H), 7,85 (s, 1 H).

(4) ácido 3-[({4-[(ciclohexil{3-metil-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

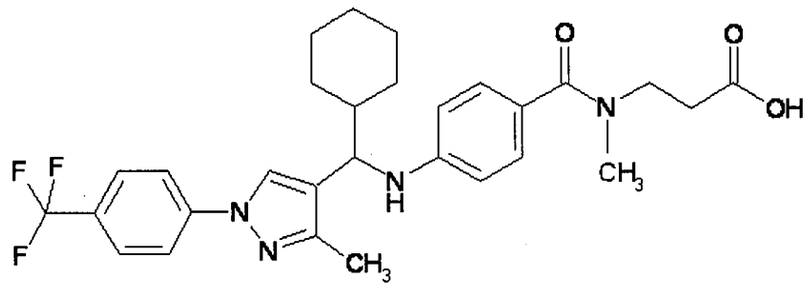
Usando ciclohexil{3-metil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-il}metanol (0,36 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,38 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (77,5 mg, 7%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,90 - 2,12 (m, 11 H), 2,26 (s, 3 H), 2,41 (t, J = 7,2 Hz, 2 H), 3,23 - 3,44 (m, 2 H), 4,22 (t, J = 7,6 Hz, 1 H), 6,36 (d, J = 7,9 Hz, 1 H), 6,60 (d, J = 8,9 Hz, 2 H), 7,52 - 7,80 (m, 4 H), 7,93 (d, J = 6,0 Hz, 2 H), 7,97 - 8,10 (s, 1H).

Ejemplo 28

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Ácido 3-[({4-[(ciclohexil{3-metil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



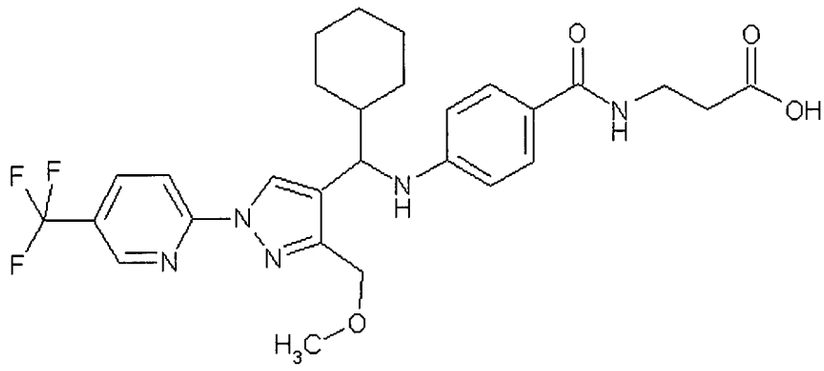
Usando ciclohexil{3-metil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-il}metanol (0,36 g) sintetizado en el Ejemplo 27(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,40 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,20 g, 35%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,81 - 2,10 (m, 11 H), 2,28 (s, 3 H), 2,42 - 2,50 (m, 2 H), 2,90 (s, 3 H), 3,52 (t, J = 7,3 Hz, 2 H), 4,18 (t, J = 7,5 Hz, 1 H), 6,26 (d, J = 7,7 Hz, 1 H), 6,59 (d, J = 8,7 Hz, 2 H), 7,11 (d, J = 8,7 Hz, 2 H), 7,80 (d, 2 H), 7,94 (d, J = 8,5 Hz, 2 H), 8,43 (s, 1 H).

Ejemplo 29

Ácido 3-[({4-[(ciclohexil{3-(metoximetil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

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(1) 3-(metoximetil)-1H-pirazol-4-carboxilato de metilo

Una mezcla de 4-metoxiacetoacetato de metilo (25,0 g) y dimetilformamida dimetilacetal (22,9 mL) se agitó a 100 °C durante 2 h y la mezcla se dejó enfriar hasta temperatura ambiente. A la mezcla de reacción se añadieron etanol (250 mL) y monohidrato de hidrazina (8,3 mL) y la mezcla se calentó a reflujo durante 12 h. Después de enfriar, la mezcla de reacción se concentró a presión reducida y se añadió agua al residuo. La mezcla se extrajo con acetato de etilo para dar un producto crudo (25,08 g) de 3-metil-1H-pirazol-4-carboxilato de metilo en forma de un sólido amarillo pálido. El presente compuesto se usó directamente para la siguiente reacción.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,51 (s, 3 H), 3,84 (s, 3 H), 4,85 (s, 2 H), 7,99 (s, 1 H).

(2) 3-(metoximetil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo

Usando 3-(metoximetil)-1H-pirazol-4-carboxilato de metilo (7,4 g) sintetizado con anterioridad y 2-cloro-5-trifluorometilpiridina (5,8 g) y de la misma manera que en el

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Ejemplo 1(4), se obtuvo el compuesto objeto del título (5,2 g, 38%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,54 (s, 3 H), 3,89 (s, 3 H), 4,83 (s, 2 H), 7,90 - 8,36 (m, 2 H), 8,70 (s, 1 H), 9,06 (s, 1 H).

(3) 3-(metoximetil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído

El 3-(metoximetil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo (5,2 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (1,9 g, 40%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,53 (s, 3 H), 4,83 (s, 2 H), 8,05 - 8,25 (m, 2 H), 8,72 (s, 1 H), 9,11 (s, 1 H), 10,10 (s, 1 H).

(4) ciclohexil{3-(metoximetil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol

El 3-(metoximetil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído (1,9 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (2,4 g, 99%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 2,25 (m, 11 H), 3,02 (d, J = 6,0 Hz, 1 H), 3,46 (s, 3 H), 4,43 (dd, J = 7,7, 6,0 Hz, 1 H), 4,52 - 4,69 (m, 2 H), 7,93 - 8,11 (m, 2 H), 8,44 (s, 1 H), 8,65 (s, 1 H).

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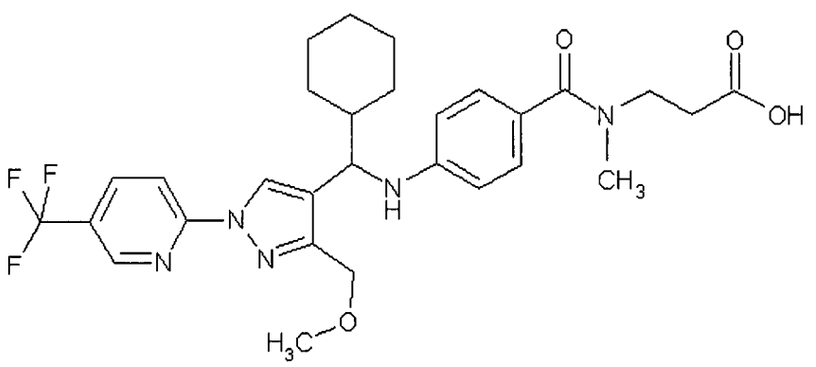
(5) ácido 3-[({4-[(ciclohexil{3-(metoximetil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

Usando ciclohexil{3-(metoximetil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (1,2 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,94 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,19 g, 10%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 1,90 - 2,10 (m, 11 H), 2,40 (t, J = 7,2 Hz, 2 H), 3,24 - 3,45 (m, 5 H), 4,28 - 4,71 (m, 3 H), 6,37 (d, J = 8,9 Hz, 1 H), 6,64 (d, J = 8,9 Hz, 2 H), 7,51 (d, J = 8,9 Hz, 2 H), 8,00 (d, J = 8,9 Hz, 2 H), 8,33 (dd, J = 9,0, 2,3 Hz, 1 H).

Ejemplo 30

Ácido 3-[({4-[(ciclohexil{3-(metoximetil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



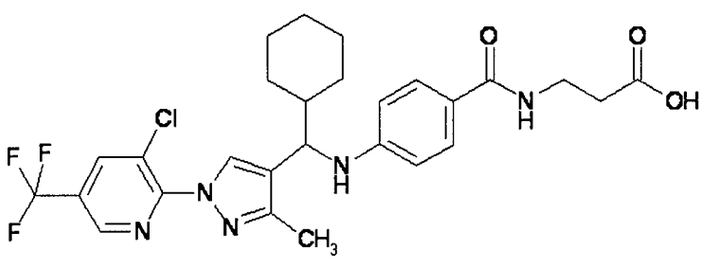
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Usando ciclohexil{3-(metoximetil)-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (1,2 g) sintetizado en el Ejemplo 29(4) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (1,0 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,17 g, 8%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,89 - 2,09 (m, 11 H), 2,40 - 2,52 (m, 2 H), 2,89 (s, 3 H), 3,33 (s, 3 H), 3,51 (t, J = 7,3 Hz, 2 H), 4,28 - 4,74 (m, 3 H), 6,27 (d, J = 8,7 Hz, 1 H), 6,64 (d, J = 8,7 Hz, 2 H), 7,09 (d, J = 8,7 Hz, 2 H), 8,01 (d, J = 8,9 Hz, 1 H), 8,33 (dd, J = 9,0, 2,3 Hz, 1 H), 8,58 (s, 1 H), 8,83 (s, 1 H).

Ejemplo 31

Ácido 3-{[(4-{[{1-[3-cloro-5-(trifluorometil)piridin-2-il]-3-metil-1H-pirazol-4-il}(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico




(1) 1-[3-cloro-5-(trifluorometil)piridin-2-il]-3-metil-1H-pirazol-4-carboxilato de metilo

Usando 3-metil-1H-pirazol-4-carboxilato de metilo (3,8 g) sintetizado en el Ejemplo 1(3) y 2,3-dicloro-5-

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trifluorometilpiridina (5,8 g) y de la misma manera que en el Ejemplo 1(4), se obtuvo el compuesto objeto del título (7,0 g, 78%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,60 (s, 3 H), 3,88 (s, 3 H), 8,16 (d, J = 1,5 Hz, 1 H), 8,67 - 8,72 (m, 2 H).

(2)1-[3-cloro-5-(trifluorometil)piridin-2-il]-3-metil-1H-pirazol-4-carbaldehído

A una solución (150 mL) de 1-[3-cloro-5-(trifluorometil)piridin-2-il]-3-metil-1H-pirazol-4-carboxilato de metilo (7,0 g) sintetizada con anterioridad en tetrahidrofurano se añadió gota a gota hidruro de diisobutilaluminio (solución toluénica 1,5 M, 58,4 mL) a 0 °C. Después de agitar durante 30 min, la mezcla de reacción se vertió en ácido clorhídrico 2 N a 0 °C y la mezcla se extrajo con acetato de etilo. El extracto se secó sobre sulfato de magnesio y el solvente se evaporó. El residuo se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (1,7 g, 27%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,63 (s, 3 H), 8,19 (s, 1 H), 8,70 - 8,73 (m, 2 H), 10,07 (s, 1 H).

(3){1-[3-cloro-5-(trifluorometil)piridin-2-il]-3-metil-1H-pirazol-4-il}(ciclohexil)metanol

El 1-[3-cloro-5-(trifluorometil)piridin-2-il]-3-metil-1H-pirazol-4-carbaldehído (1,7 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (1,5 g, 66%) en forma de un aceite.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 2,02 (m, 11 H), 2,39 (s, 3 H), 4,47 (d, J = 7,2 Hz, 1 H), 8,05 - 8,14 (m, 1 H), 8,18 (s, 1 H), 8,66 (s, 2 H).

(4) ácido 3-{[(4-{[{1-[3-cloro-5-(trifluorometil)piridin-2-il]-3-metil-1H-pirazol-4-il}(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico

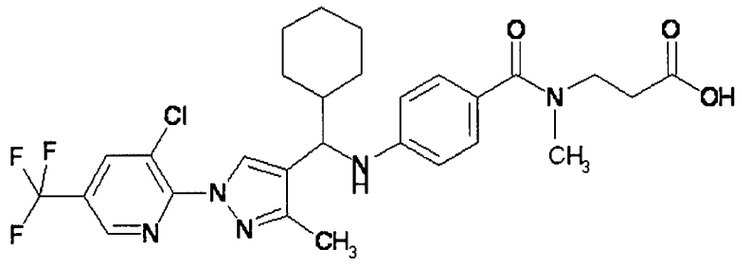
Usando el {1-[3-cloro-5-(trifluorometil)piridin-2-il]-3-metil-1H-pirazol-4-il}(ciclohexil)metanol (0,74 g) sintetizado con anterioridad y el 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,57 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,11 g, 10%) en forma de un sólido amorfo de color amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 - 1,98 (m, 11 H), 2,37 (s, 3 H), 2,50 - 2,72 (m, 2 H), 3,44 - 3,75 (m, 2 H), 4,24 (d, J = 6,2 Hz, 1 H), 6,51 (d, J = 8,1 Hz, 2 H), 6,66 (br. s., 1 H), 6,89 (br. s., 1 H), 7,52 (d, J = 8,1 Hz, 2 H), 7,98 - 8,20 (m, 2 H), 8,60 (s, 1 H).

Ejemplo 32

Ácido 3-{[(4-{[{1-[3-cloro-5-(trifluorometil)piridin-2-il]-3-metil-1H-pirazol-4-il}(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico

1025



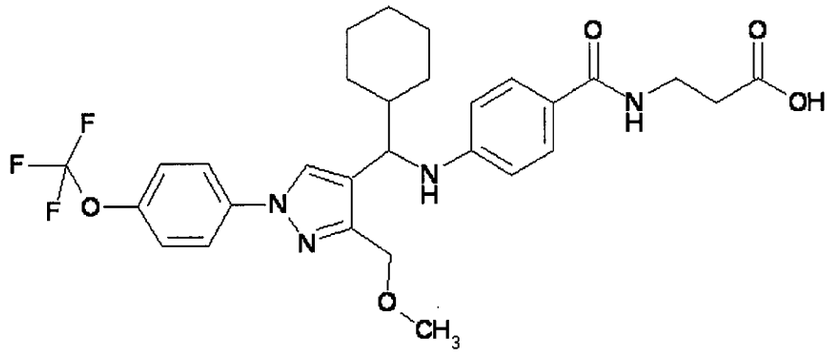
Usando el {1-[3-cloro-5-(trifluorometil)piridin-2-il]-3-metil-1H-pirazol-4-il}(ciclohexil)metanol (0,74 g) sintetizado en el Ejemplo 31(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,60 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (54,4 mg, 5%) en forma de un sólido amorfo de color amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,98 (m, 11 H), 2,36 (s, 3 H), 2,58 - 2,74 (m, 2 H), 3,04 (s, 3 H), 3,59 - 3,82 (m, 2 H), 4,23 (d, J = 6,0 Hz, 1 H), 6,55 (d, J = 8,5 Hz, 2 H), 7,01 (br. s., 1 H), 7,21 (d, J = 8,5 Hz, 2 H), 8,08 (s, 1 H), 8,13 (s, 1 H), 8,63 (s, 1 H).

Ejemplo 33

Ácido 3-[({4-[(ciclohexil{3-(metoximetil)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

1026



1) 3-(metoximetil)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carboxilato de metilo

Usando 4-metoxiacetoacetato de metilo (3,2 g), dimetilformamida dimetilacetal (2,9 mL) y clorhidrato de 4-trifluorometoxifenilhidrazina (5,0 g) y de la misma manera que en el Ejemplo 15(1), se obtuvo el compuesto objeto del título (3,4 g, 47%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,46 (s, 3 H), 3,89 (s, 3 H), 4,70 (s, 2 H), 7,37 (d, J = 9,0 Hz, 2H), 7,73 (d, J = 9,0 Hz, 2H), 8,08 (s, 1 H).

(2) 3-(metoximetil)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carbaldehído

El 3-(metoximetil)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carboxilato de metilo (3,4 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (2,9 g, 93%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,41 (s, 3 H), 4,70 (s, 2 H), 7,37 - 8,08 (m, 5 H), 10,00 (s, 1 H).

(3) ciclohexil{3-(metoximetil)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metanol

1027

El 3-(metoximetil)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carbaldehído (2,9 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (2,8 g, 77%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,73 - 2,28 (m, 11 H), 3,41 (s, 3 H), 4,30 - 4,53 (m, 3 H), 7,33 (d, J = 8,5 Hz, 2 H), 7,55 - 7,75 (m, 3 H).

(4) ácido 3-[({4-[(ciclohexil{3-(metoximetil)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

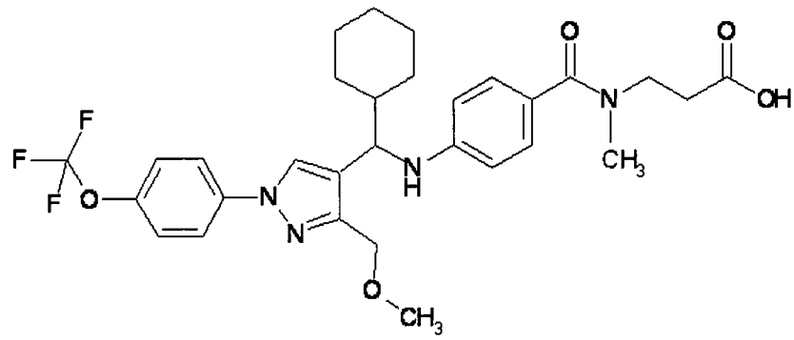
Usando ciclohexil{3-(metoximetil)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metanol (0,75 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,55 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,43 g, 39%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,90 - 2,08 (m, 11 H), 2,43 (t, J = 7,1 Hz, 2 H), 3,25 - 3,49 (m, 5 H), 4,29 - 4,31 (m, 1 H), 4,39 - 4,59 (m, 2 H), 6,43 (d, J = 8,5 Hz, 1 H), 6,63 (d, J = 8,9 Hz, 2 H), 7,45 - 7,58 (m, 4 H), 7,63 - 7,77 (m, 3 H), 7,94 - 8,09 (m, 1 H).

Ejemplo 34

Ácido 3-[({4-[(ciclohexil{3-(metoximetil)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

1028



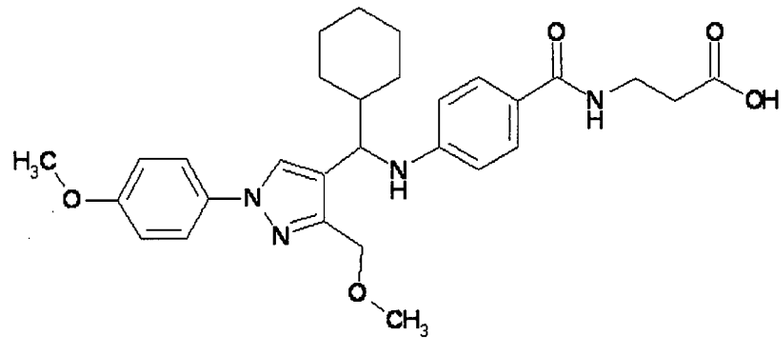
Usando ciclohexil{3-(metoximetil)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metanol (0,75 g) sintetizado en el Ejemplo 33(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,59 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,42 g, 39%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,87 - 2,12 (m, 11 H), 2,40 - 2,50 (m, 2 H), 2,90 (s, 3 H), 3,31 (s, 3 H), 3,52 (t, J = 7,2 Hz, 2 H), 4,21 - 4,36 (m, 1 H), 4,36 - 4,59 (m, 2 H), 6,32 (d, J = 8,7 Hz, 1 H), 6,62 (d, J = 8,7 Hz, 2 H), 7,09 (d, J = 8,5 Hz, 2 H), 7,51 (d, J = 8,5 Hz, 2 H), 7,64 - 7,79 (m, 3 H).

Ejemplo 35

Ácido 3-({[4-({ciclohexil[3-(metoximetil)-1-(4-metoxifenil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico

1029



(1) 3-(metoximetil)-1-(4-metoxifenil)-1H-pirazol-4-carboxilato de metilo

Usando 4-metoxiacetoacetato de metilo (5,8 g), dimetilformamida dimetilacetal (5,4 mL) y clorhidrato de 4-metoxifenilhidrazina (7,0 g) y de la misma manera que en el Ejemplo 15(1), se obtuvo el compuesto objeto del título (5,5 g, 50%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,42 (s, 3 H), 3,87 (s, 3 H), 3,88 (s, 3 H), 4,64 (s, 2 H), 7,00 (d, J = 9,0 Hz, 2H), 7,53 (d, J = 9,0 Hz, 2H), 8,05 (s, 1 H).

(2) 3-(metoximetil)-1-(4-metoxifenil)-1H-pirazol-4-carbaldehído

El 3-(metoximetil)-1-(4-metoxifenil)-1H-pirazol-4-carboxilato de metilo (2,8 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (2,0 g, 83%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,42 (s, 3 H), 3,87 (s, 3 H), 4,64 (s, 2 H), 7,00 - 8,05 (m, 5 H), 10,00 (s, 1 H).

1030

(3) ciclohexil[3-(metoximetil)-1-(4-metoxifenil)-1H-pirazol-4-il]metanol

El 3-(metoximetil)-1-(4-metoxifenil)-1H-pirazol-4-carbaldehído (2,0 g) sintetizada con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (2,1 g, 77%) en forma de un sólido blanco.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,73 - 2,28 (m, 11 H), 3,36 (s, 3 H), 3,86 (s, 3 H), 4,30 - 4,53 (m, 3 H), 6,97 (d, J = 8,9 Hz, 2 H), 7,44 (d, J = 8,9 Hz, 2 H), 7,59 (s, 1H).

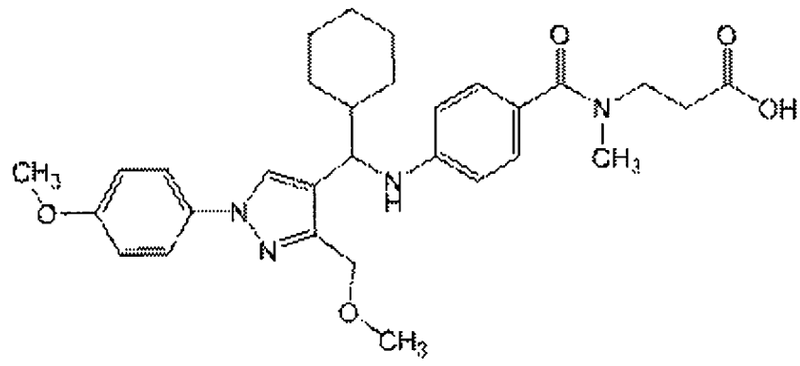
(4) ácido 3-({[4-({ciclohexil[3-(metoximetil)-1-(4-metoxifenil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico

Usando ciclohexil[3-(metoximetil)-1-(4-metoxifenil)-1H-pirazol-4-il]metanol (0,75 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,54 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,39 g, 33%) en forma de un sólido blanco.
$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,89 - 2,11 (m, 11 H), 2,44 (t, J = 7,2 Hz, 2 H), 3,32 - 3,46 (m, 2 H), 3,80 (s, 3 H), 4,22 - 4,56 (m, 3 H), 6,40 (d, J = 8,7 Hz, 1 H), 6,62 (d, J = 8,9 Hz, 2 H), 7,04 (d, J = 9,0 Hz, 2 H), 7,36 - 7,55 (m, 4 H), 7,57 (s, 1 H), 8,01 (s, 1 H).

Ejemplo 36

Ácido 3-[{[4-({ciclohexil[3-(metoximetil)-1-(4-metoxifenil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

1031



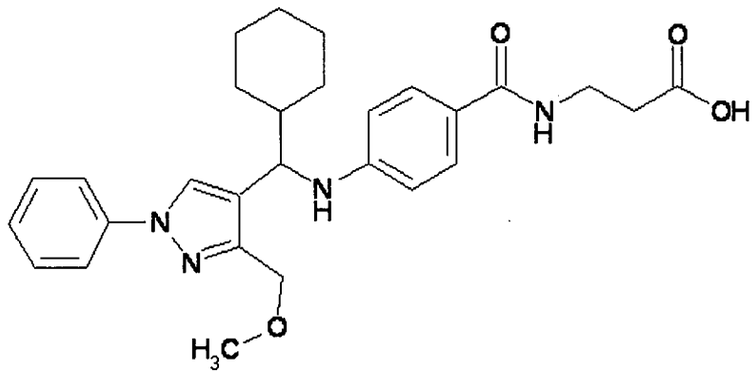
Usando ciclohexil[3-(metoximetil)-1-(4-metoxifenil)-1H-pirazol-4-il]metanol (0,75 g) sintetizado en el Ejemplo 35(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,57 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,44 g, 36%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,90 - 2,12 (m, 11 H), 2,42 - 2,50 (m, 2 H), 2,91 (s, 3 H), 3,26 (s, 3 H), 3,52 (t, J = 7,4 Hz, 2 H), 3,80 (s, 3 H), 4,14 - 4,54 (m, 3 H), 6,29 (d, J = 8,5 Hz, 1 H), 6,62 (d, J = 8,7 Hz, 2 H), 6,97 - 7,19 (m, 4 H), 7,44 (d, J = 8,9 Hz, 2 H), 7,58 (s, 1 H).

Ejemplo 37

Ácido 3-({[4-({ciclohexil[3-(metoximetil)-1-fenil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico

1032



(1) 3-(metoximetil)-1-fenil-1H-pirazol-4-carboxilato de metilo

Usando 4-metoxiacetoacetato de metilo (7,9 g), dimetilformamida dimetilacetal (7,2 mL) y clorhidrato de fenilhidrazina (5,8 g) y de la misma manera que en el Ejemplo 15(1), se obtuvo el compuesto objeto del título (7,3 g, 55%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,44 (s, 3 H), 3,89 (s, 3 H), 4,68 (s, 2 H), 7,30 - 7,70 (m, 5 H), 8,08 (s, 1 H).

(2) 3-(metoximetil)-1-fenil-1H-pirazol-4-carbaldehído

El 3-(metoximetil)-1-fenil-1H-pirazol-4-carboxilato de metilo (3,5 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(5) para dar el compuesto objeto del título (2,5 g, 82%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,45 (s, 3 H), 4,67 (s, 2 H), 7,40 - 8,20 (m 6 H), 10,08 (s, 1 H).

(3) ciclohexil[3-(metoximetil)-1-fenil-1H-pirazol-4-il]metanol

1033

3-(Metoximetil)-1-fenil-1H-pirazol-4-carbaldehído (2,5 g) sintetizado con anterioridad se trató de la misma manera que en el Ejemplo 1(6) para dar el compuesto objeto del título (3,1 g, 75%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,73 - 2,40 (m, 11 H), 3,38 (s, 3 H), 4,40 (s, 2 H), 4,42 - 4,55 (m, 1 H), 7,27 - 7,70 (m, 6H).

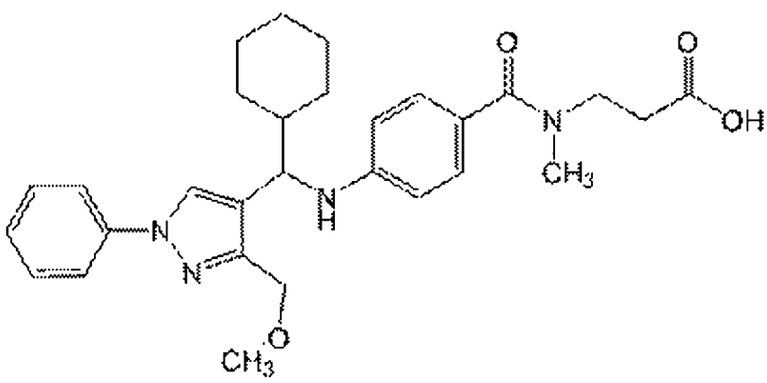
(4) ácido 3-({[4-({ciclohexil[3-(metoximetil)-1-fenil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico

Usando ciclohexil[3-(metoximetil)-1-fenil-1H-pirazol-4-il]metanol (0,50 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,39 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,37 g, 46%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 - 2,17 (m, 11 H), 2,58 - 2,78 (m, 2 H), 3,34 (s, 3 H), 3,58 - 3,76 (m, 2 H), 4,21 - 4,51 (m, 3 H), 6,51 - 6,71 (m, 3 H), 7,36 - 7,74 (m, 8 H).

Ejemplo 38

Ácido 3-[{[4-({ciclohexil[3-(metoximetil)-1-fenil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



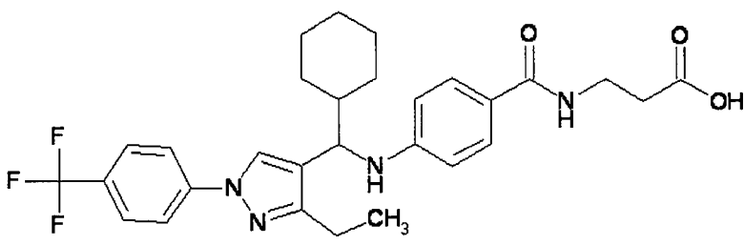
1034

Usando ciclohexil[3-(metoximetil)-1-fenil-1H-pirazol-4-il]metanol (0,50 g) sintetizado en el Ejemplo 37(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,42 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,33 g, 39%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 - 2,11 (m, 11 H), 2,61 - 2,79 (m, 2 H), 3,07 (s, 3 H), 3,34 (s, 3 H), 3,72 (t, J = 6,5 Hz, 2 H), 4,25 - 4,46 (m, 3 H), 6,57 (d, J = 8,5 Hz, 2 H), 7,35 - 7,61 (m, 8 H).

Ejemplo 39

Ácido 3-[({4-[(ciclohexil{3-etil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico




(1) 3-etil-1H-pirazol-4-carboxilato de metilo

Usando 3-oxopentanoato de metilo (6,5 g) y de la misma manera que en el Ejemplo 1(3), se obtuvo el compuesto objeto del título (7,0 g, 91%) en forma de un aceite.

1035

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,32 (t, J = 7,6 Hz, 3 H), 3,02 (q, J = 7,6 Hz, 2 H), 3,84 (s, 3 H), 7,96 (s, 1 H), 11,28 (br. s., 1 H).

(2) 3-etil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-carboxilato de metilo

Usando 3-etil-1H-pirazol-4-carboxilato de metilo (4,6 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 17(1), se obtuvo el compuesto objeto del título (6,0 g, 67%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,33 (t, J = 7,4 Hz, 3 H), 2,99 (q, J = 7,5 Hz, 2 H), 3,87 (s, 3 H), 7,71-7,74 (m, 2 H), 7,82-7,85 (m, 2 H), 8,41 (s, 1 H).

(3) 3-etil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-carbaldehído

Usando 3-etil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-carboxilato de metilo (6,0 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(5), se obtuvo el compuesto objeto del título (4,2 g, 78%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,37 (t, J = 7,4 Hz, 3 H), 3,00 (q, J = 7,4 Hz, 2 H), 7,74-7,77 (m, 2H), 7,84-7,87 (m, 2 H), 8,42 (s, 1 H), 10,03 (s, 1 H).

(4) ciclohexil{3-etil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-il}metanol

Usando 3-etil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-carbaldehído (1,6 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (1,9 g, 91%) en forma de un sólido blanco.

1036

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86-1,43 (m, 8 H), 1,52-1,90 (m, 5 H), 2,05 (br.s, 1 H), 2,72 (q, J = 7,5 Hz, 2 H), 4,46 (dd, J = 7,2, 3,0 Hz, 1 H), 7,60-7,71 (m, 2 H), 7,71-7,82 (m, 2 H), 7,86 (s, 1 H).

(5) ácido 3-({4-[(ciclohexil{3-etil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-il}metil)amino]benzoil}amino)propanoico

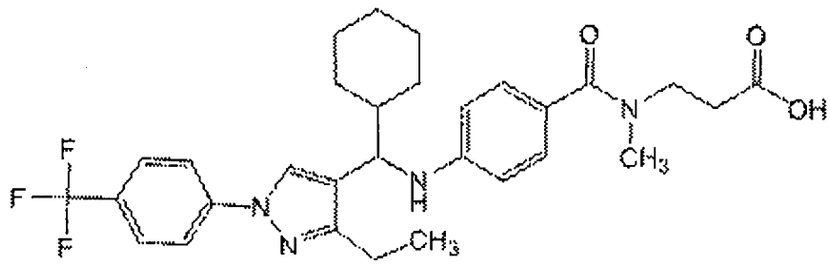
Usando ciclohexil{3-etil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-il}metanol (0,90 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,75 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (82 mg, 6%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,09-1,32 (m, 8 H), 1,45-1,83 (m, 5 H), 1,93-2,11 (m, 1 H), 2,37 (t, J = 7,0 Hz, 2 H), 2,68 (qd, J = 7,5, 4,0 Hz, 2 H), 3,35 (q, J = 5,7 Hz, 2 H), 4,23 (t, J = 7,8 Hz, 1 H), 6,33 (d, J = 7,9 Hz, 1 H), 6,60 (d, J = 8,7 Hz, 2 H), 7,52 (d, J = 8,9 Hz, 2 H), 7,81 (d, J = 8,7 Hz, 2 H), 7,87-7,98 (m, 2 H), 7,98-8,12 (m, 1 H), 8,43 (s, 1 H).

Ejemplo 40

Ácido 3-[({4-[(ciclohexil{3-etil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

1037



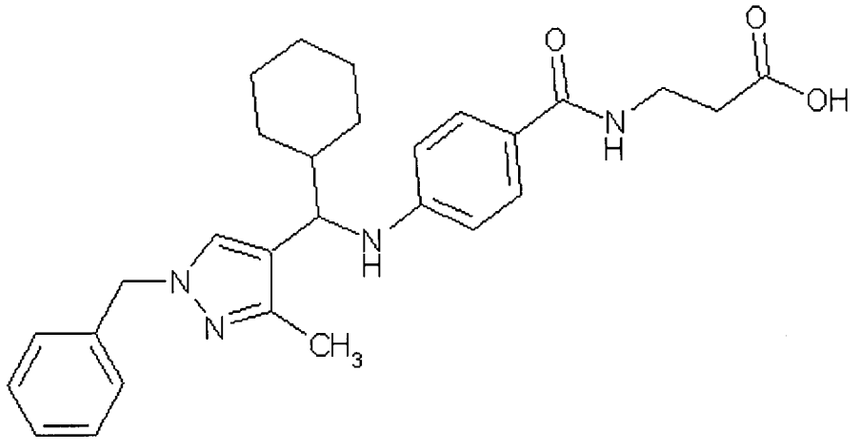
Usando ciclohexil{3-etil-1-[4-(trifluorometil)fenil]-1H-pirazol-4-il}metanol (0,90 g) sintetizado en el Ejemplo 39(4) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,75 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (85 mg, 6%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,88-1,24 (m, 8 H), 1,46-1,80 (m, 5 H), 1,92-2,09 (m, 1 H), 2,46 (t, J = 7,5 Hz, 2 H), 2,68 (qd, J = 7,5, 3,3 Hz, 2 H), 2,98 (s, 3 H), 3,50 (t, J = 7,2 Hz, 2 H), 4,20 (t, J = 7,4 Hz, 1 H), 6,22 (d, J = 7,7 Hz, 1 H), 6,60 (d, J = 8,5 Hz, 2 H), 7,10 (d, J = 8,7 Hz, 2 H), 7,81 (d, J = 8,7 Hz, 2 H), 7,86-8,05 (m, 2 H), 8,43 (s, 1 H).

Ejemplo 41

Ácido 3-{[(4-{[(1-bencil-3-metil-1H-pirazol-4-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico

1038



(1) 1-bencil-3-metil-1H-pirazol-4-carboxilato de metilo

El 3-metil-1H-pirazol-4-carboxilato de metilo (5,1 g) sintetizado en el Ejemplo 1(3) se disolvió en dimetilformamida (50 mL), se añadieron carbonato de potasio (5,3 g) y bromuro de bencilo (4,6 mL) a temperatura ambiente y la mezcla se agitó durante la noche. La mezcla de reacción se vertió en agua y la mezcla se extrajo con éter dietílico. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (5,9 g, 71%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,48 (s, 3 H), 3,78 (s, 3 H), 5,22 (s, 2 H), 6,96 - 7,45 (m, 5 H), 7,77 (s, 1 H).

(2) 1-bencil-3-metil-1H-pirazol-4-carbaldehído

Usando 1-bencil-3-metil-1H-pirazol-4-carboxilato de metilo (5,9 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(5), se obtuvo el compuesto objeto del título (5,0 g, 96%) en forma de un aceite.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,50 (s, 3 H), 5,25 (s, 2 H), 6,96 - 7,45 (m, 5 H), 7,76 (s, 1 H), 9,85 (s, 1H).

(3) (1-bencil-3-metil-1H-pirazol-4-il)(ciclohexil)metanol

Usando 1-bencil-3-metil-1H-pirazol-4-carbaldehído (5,0 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (3,3 g, 47%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,75 - 1,97 (m, 11 H), 2,25 (s, 3 H), 4,34 (d, J = 7,4, 3,3 Hz, 1 H), 5,20 (s, 2H), 7,00 - 7,50 (m, 6 H).

(4) ácido 3-{[(4-{[(1-bencil-3-metil-1H-pirazol-4-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico

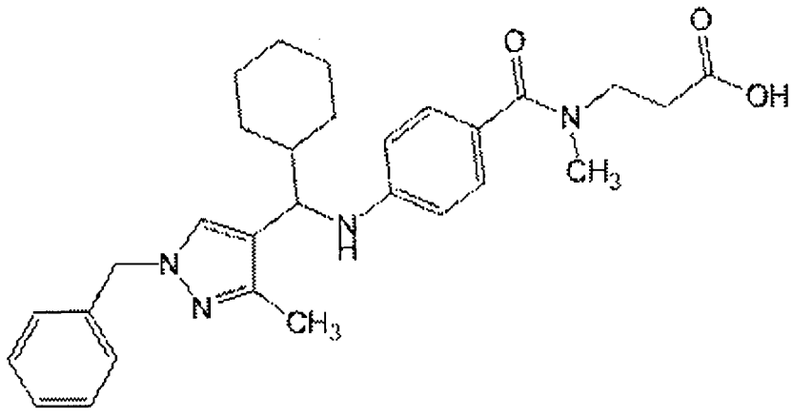
Usando (1-bencil-3-metil-1H-pirazol-4-il)(ciclohexil)metanol (1,0 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,62 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (28,6 mg, 4%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,77 - 2,01 (m, 11 H), 2,12 (s, 3 H), 2,38 - 2,46 (m, 2 H), 3,35 - 3,44 (m, 2 H), 3,99 - 4,21 (m, 1 H), 5,11 - 5,19 (m, 2 H), 6,25 (d, J = 9,0 Hz, 1 H), 6,52 (d, J = 8,7 Hz, 2 H), 7,04 (dd, J = 7,5, 1,9 Hz, 2 H), 7,25 - 7,60 (m, 6 H), 7,99 (s, 1 H).

Ejemplo 42

Ácido 3-{[(4-{[(1-bencil-3-metil-1H-pirazol-4-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico

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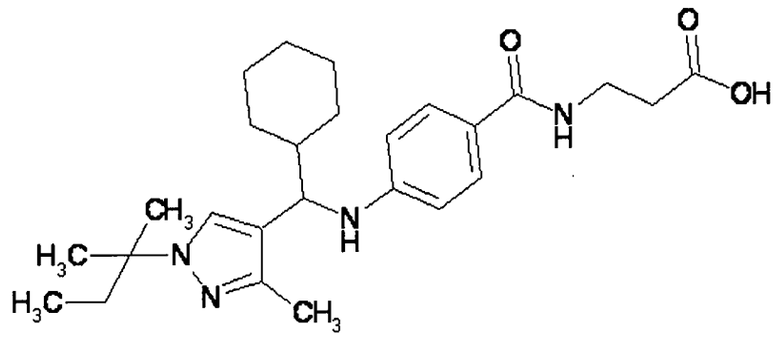
Usando (1-bencil-3-metil-1H-pirazol-4-il)(ciclohexil)metanol (0,65 g) sintetizado en el Ejemplo 41(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,65 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (18,2 mg, 2%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 1,14 - 2,00 (br. s., 11 H), 2,13 (s, 3 H), 2,38 - 2,46 (m, 2 H), 2,90 (s, 3 H), 3,42 - 3,60 (m, 2 H), 4,00 - 4,17 (m, 1 H), 5,16 (s, 2 H), 6,17 (d, J = 6,0 Hz, 1 H), 6,52 (d, J = 8,5 Hz, 2 H), 6,95 - 7,36 (m, 7 H), 7,52 (s, 1 H).

Ejemplo 43

Ácido 3-({[4-({ciclohexil[1-(1,1-dimetilpropil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico

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(1) 1-(1,1-dimetilpropil)-3-metil-1H-pirazol-4-carboxilato de metilo

El 3-metil-1H-pirazol-4-carboxilato de metilo (10,8 g) sintetizado en el Ejemplo 1(3) se disolvió en acetonitrilo (100 mL), se añadieron 2-metil-2-buteno (16,3 mL) y ácido p-toluensulfónico monohidratado (4,4 g) y la mezcla se agitó en un tubo sellado a 120 °C durante 4 h. La mezcla de reacción se vertió en solución acuosa de hidrógeno-carbonato de sodio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (4,6 g, 29%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,68 (t, J = 7,5 Hz, 3 H), 1,53 (s, 6 H), 1,88 (q, J = 7,5 Hz, 2 H), 2,46 (s, 3 H), 3,80 (s, 3 H), 7,90 (s, 1 H).

(2) 1-(1,1-dimetilpropil)-3-metil-1H-pirazol-4-carbaldehído

Usando 1-(1,1-dimetilpropil)-3-metil-1H-pirazol-4-carboxilato de metilo (4,6 g) sintetizado con anterioridad y

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de la misma manera que en el Ejemplo 1(5), se obtuvo el compuesto objeto del título (3,0 g, 73%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,68 (t, J = 7,5 Hz, 3 H), 1,53 (s, 6 H), 1,88 (q, J = 7,5 Hz, 2 H), 2,46 (s, 3 H), 7,90 (s, 1 H), 9,85 (s, 1H).

(3) ciclohexil[1-(1,1-dimetilpropil)-3-metil-1H-pirazol-4-il]metanol

Usando 1-(1,1-dimetilpropil)-3-metil-1H-pirazol-4-carbaldehído (3,0 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (1,4 g, 32%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,67 (t, J = 7,4 Hz, 3 H), 0,88 - 2,00 (m, 13 H), 1,52 (s, 6 H), 2,24 (s, 3 H), 3,61 (br. s., 1 H), 4,34 (dd, J = 7,6, 2,0 Hz, 1 H), 7,34 (s, 1 H).

(4) ácido 3-({[4-({ciclohexil[1-(1,1-dimetilpropil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico

Usando ciclohexil[1-(1,1-dimetilpropil)-3-metil-1H-pirazol-4-il]metanol (1,0 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,67 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,41 g, 46%) en forma de un sólido blanco.

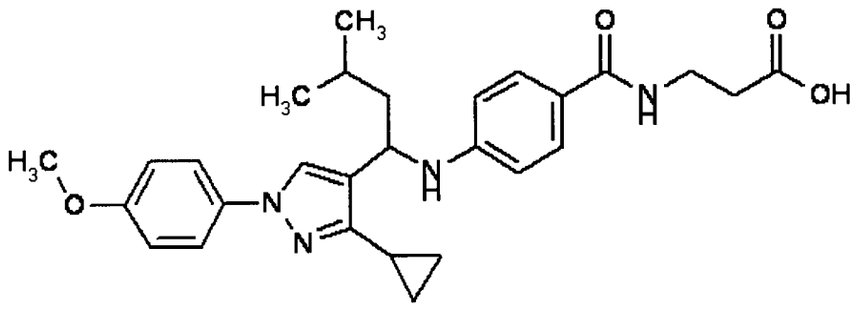
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,56 (t, J = 7,6 Hz, 3 H), 0,88 - 1,35 (m, 5 H), 1,48 (s, 6 H), 1,55 - 1,98 (m, 8 H), 2,26 (s, 3 H), 2,67 (t, J = 5,9 Hz, 2 H), 3,68 (q, J = 5,8 Hz, 2 H), 4,12 (d, J = 6,1 Hz, 1 H), 6,46 (d, J = 8,7 Hz, 2 H),

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6,66 (t, J = 6,2 Hz, 1 H), 7,19 (s, 1 H), 7,53 (d, J = 9,1 Hz, 2 H).

Ejemplo 44

Ácido 3-({[4-({1-[3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-il]-3-metilbutil}amino)fenil]carbonil}amino)propanoico



(1) 3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-carboxilato de metilo

Usando 3-ciclopropil-3-oxopropanoato de metilo (3,7 g), dimetilformamida dimetilacetal (3,6 mL) y p-metoxifenilmonohidrato de hidrazina (4,7 g) y de la misma manera que en el Ejemplo 15(1), se obtuvo el compuesto objeto del título (5,9 g, 84%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,60 - 1,01 (m, 4 H), 1,86 - 2,01 (m, 1 H), 3,85 (s, 3 H), 3,87 (s, 3 H), 6,98 (d, J = 8,9 Hz, 2 H), 7,41 (d, J = 9,0 Hz, 2 H), 7,98 (s, 1 H).

(2) 3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-carbaldehído

Usando 3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-carboxilato de metilo (5,9 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(5), se obtuvo el

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compuesto objeto del título (3,6 g, 68%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,73 - 1,10 (m, 4 H), 1,87 - 2,07 (m, 1 H), 3,88 (s, 3 H), 7,01 (d, J = 8,9 Hz, 2 H), 7,44 (d, J = 8,9 Hz, 2 H), 8,03 (s, 1 H), 10,03 (s, 1 H).

(3) 1-[3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-il]-3-metilbutan-1-ol

El 3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-carbaldehído (1,8 g) sintetizado con anterioridad se disolvió en tetrahidrofurano (10 mL), se añadió bromuro de isobutilmagnesio (solución 1 M de tetrahidrofurano, 12 mL) y se añadió gota a gota a 0 °C. De la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (1,8 g, 82%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,36 - 0,91 (m, 5 H), 0,99 (d, J = 6,4 Hz, 6 H), 1,48 - 1,97 (m, 3 H), 3,86 (s, 3 H), 4,89 - 5,05 (m, 1 H), 6,96 (d, J = 9,0 Hz, 2 H), 7,42 (d, J = 9,0 Hz, 2 H), 7,60 (s, 1 H).

(4) ácido 3-({[4-({1-[3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-il]-3-metilbutil}amino)fenil]carbonil}amino)propanoico

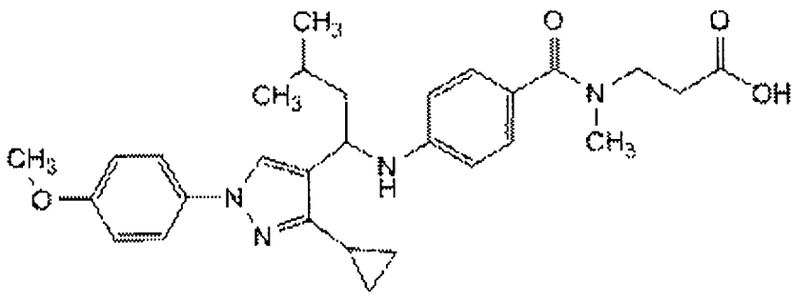
Usando 1-[3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-il]-3-metilbutan-1-ol (0,5 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,31 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (23 mg, 3%) en forma de un sólido blanco.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,42 - 0,84 (m, 4 H), 0,99 (dd, J = 13,8, 5,7 Hz, 6 H), 1,60 -1,80 (m, 4 H), 2,60 - 2,65 (m., 2 H), 3,64 - 3,66 (m., 2 H), 3,84 (s, 3 H), 4,69 (s, 1 H), 6,55 (d, J = 8,5 Hz, 2 H), 6,70 (br. s., 1 H), 6,94 (d, J = 8,8 Hz, 2 H), 7,39 (d, J = 8,8 Hz, 2 H), 7,50 (s, 1 H), 7,58 (d, J = 8,5 Hz, 2 H).

Ejemplo 45

Ácido 3-[{[4-({1-[3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-il]-3-metilbutil}amino)fenil]carbonil}(metil)amino]propanoico



Usando 1-[3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-il]-3-metilbutan-1-ol (0,5 g) sintetizado en el Ejemplo 44(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,33 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (80 mg, 9%) en forma de un sólido blanco.

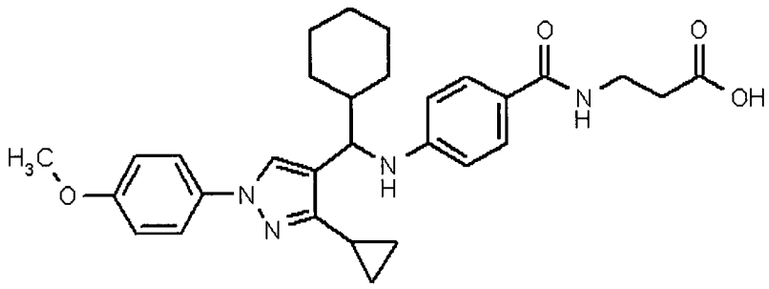
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,34 - 0,90 (m, 4 H), 0,99 (dd, J = 14,0, 4,8 Hz, 6 H), 1,70 - 2,00 (m, 4 H), 2,71 (br. s., 2 H), 3,10 (s, 3 H), 3,74 (s, 2 H), 3,85 (s, 3 H), 4,68 (br.

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s., 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,95 (dd, J = 8,7, 1,3 Hz, 2 H), 7,31 - 7,40 (m, 4 H), 7,50 (s, 1 H).

Ejemplo 46

Ácido 3-({[4-({ciclohexil[3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico



(1) ciclohexil[3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-il]metanol

Usando 3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-carbaldehído (1,8 g) sintetizado en el Ejemplo 44(2) y de la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (2,1 mg, 85%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,29 - 2,27 (m, 16 H), 3,86 (s, 3 H), 4,57 (dd, J = 8,1, 4,0 Hz, 1 H), 6,96 (d, J = 9,0 Hz, 2 H), 7,42 (d, J = 8,9 Hz, 2 H), 7,59 (s, 1 H).

(2) ácido 3-({[4-({ciclohexil[3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico

Usando ciclohexil[3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-il]metanol (0,5 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,36 g)

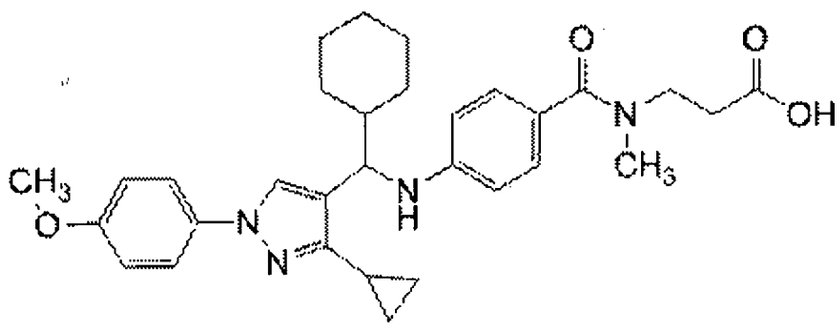
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sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (43 mg, 5%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,30 - 2,20 (m., 16 H), 2,65 (br. s., 2 H), 3,66 (br. s., 2 H), 3,85 (s, 3 H), 4,45 (d, J = 7,2 Hz, 1 H), 6,55 (d, J = 8,9 Hz, 2 H), 6,60 - 6,69 (m, 1 H), 6,94 (d, J = 9,0 Hz, 2 H), 7,38 (d, J = 9,0 Hz, 2 H), 7,47 (s, 1 H), 7,56 (d, J = 8,9 Hz, 2 H).

Ejemplo 47

Ácido 3-[{[4-({ciclohexil[3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico




Usando ciclohexil[3-ciclopropil-1-(4-metoxifenil)-1H-pirazol-4-il]metanol (0,5 g) sintetizado en el Ejemplo 46(1) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,38 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,11 g, 14%) en forma de un sólido blanco.

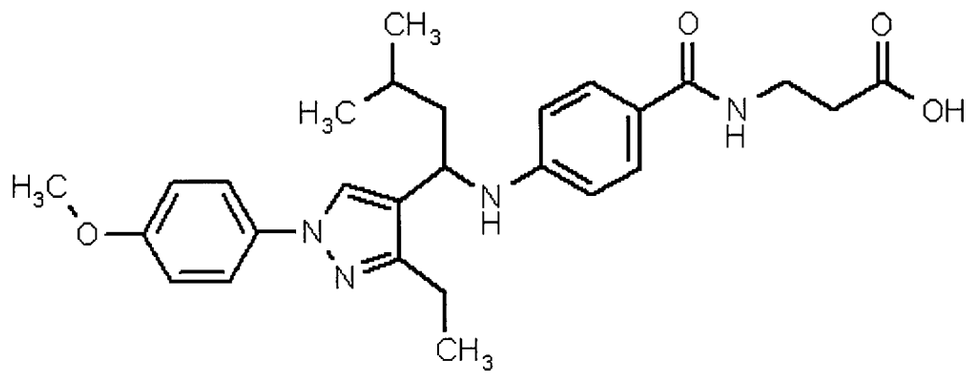
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,31 - 2,00 (m, 16 H), 2,70 - 2,74 (m, 2 H), 3,10 (s, 3 H), 3,74 (t, J = 6,5 Hz, 2 H), 3,85

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(s, 3 H), 4,45 (d, J = 6,8 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,95 (d, J = 9,0 Hz, 2 H), 7,30 - 7,42 (m, 4 H), 7,47 (s, 1 H).

Ejemplo 48

Ácido 3-({[4-({1-[3-etil-1-(4-metoxifenil)-1H-pirazol-4-il]-3-metilbutil}amino)fenil]carbonil}amino)propanoico



(1) 3-etil-1-(4-metoxifenil)-1H-pirazol-4-carboxilato de metilo

Usando 3-oxopentanoato de metilo (3,3 g), dimetilformamida dimetilacetal (3,6 mL) y p-metoxifenilmonohidrato de hidrazina (4,7 g) y de la misma manera que en el Ejemplo 15(1), se obtuvo el compuesto objeto del título (6,0 g, 84%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,14 (t, J = 7,5 Hz, 3 H), 2,92 (q, J = 7,3 Hz, 2 H), 3,86 (s, 3 H), 3,87 (s, 3 H), 7,00 (d, J = 9,0 Hz, 2 H), 7,31 (d, J = 9,0 Hz, 2 H), 7,99 (s, 1 H).

(2) 3-etil-1-(4-metoxifenil)-1H-pirazol-4-carbaldehído

Usando 3-etil-1-(4-metoxifenil)-1H-pirazol-4-carboxilato de metilo (6,0 g) sintetizado con anterioridad y de la misma

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manera que en el Ejemplo 1(5), se obtuvo el compuesto objeto del título (4,0 g, 76%) en forma de un sólido blanco.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,18 (t, J = 7,5 Hz, 3 H), 2,92 (q, J = 7,5 Hz, 2 H), 3,88 (s, 3 H), 6,91 - 7,08 (m, 2 H), 7,12 - 7,22 (m, 2 H), 7,33 (d, J = 9,0 Hz, 2 H), 8,03 (s, 1 H), 9,97 (s, 1 H).
(3)1-[3-etil-1-(4-metoxifenil)-1H-pirazol-4-il]-3-metilbutan-1-ol

Usando 3-etil-1-(4-metoxifenil)-1H-pirazol-4-carbaldehído (2,1 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (1,2 g, 47%) en forma de un sólido blanco.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 (6 H, d, J = 6,4 Hz), 1,06 (3 H, t, J = 7,6 Hz), 1,50 (1 H, d, J = 4,3 Hz), 1,59 - 1,96 (3 H, m), 2,70 (2 H, q, J = 7,5 Hz), 3,86 (3 H, s), 4,77 (1 H, dt, J = 8,1, 5,1 Hz), 6,97 (2 H, d, J = 8,9 Hz), 7,31 (2 H, d, J = 8,9 Hz), 7,60 (1 H, s).
(4) ácido 3-({[4-({1-[3-etil-1-(4-metoxifenil)-1H-pirazol-4-il]-3-metilbutil}amino)fenil]carbonil}amino)propanoico

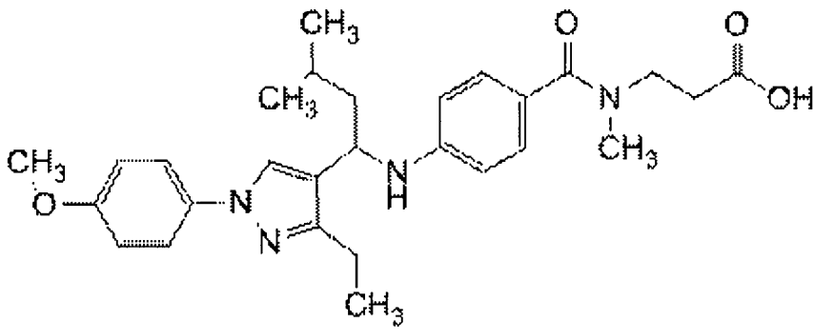
Usando en 1-[3-etil-1-(4-metoxifenil)-1H-pirazol-4-il]-3-metilbutan-1-ol (0,5 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,41 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,2 g, 25%) en forma de un sólido blanco.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,20 (m, 9 H), 1,70 - 1,90 (m, 3 H), 2,63 (d, J = 6,0 Hz, 4 H), 3,67 (d, J = 5,5 Hz, 2 H), 3,84 (s, 3 H), 4,48 (t, J = 6,8 Hz, 1 H), 6,58 (d,

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J = 8,1 Hz, 2 H), 6,65 - 6,80 (m, 1 H), 6,95 (d, J = 8,9 Hz, 2 H), 7,25 - 7,79 (m, 5 H).

Ejemplo 49

Ácido 3-[{[4-({1-[3-etil-1-(4-metoxifenil)-1H-pirazol-4-il]-3-metilbutil}amino)fenil]carbonil}(metil)amino]propanoico

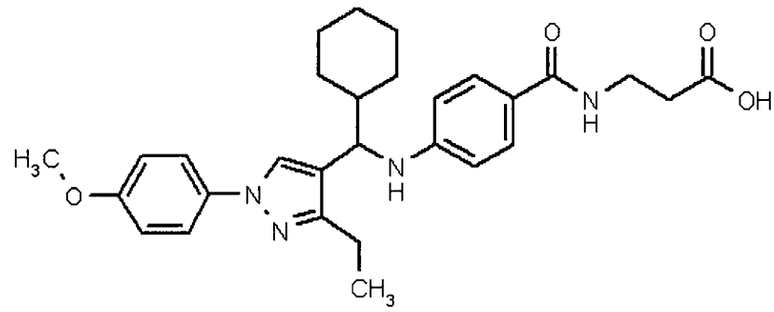


Usando 1-[3-etil-1-(4-metoxifenil)-1H-pirazol-4-il]-3-metilbutan-1-ol (0,5 g) sintetizado en el Ejemplo 48(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,44 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,1 g, 12%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 1,09 (m, 9 H), 1,70 - 1,80 (m, 3 H), 2,59 - 2,81 (m, 4 H), 3,11 (s, 3 H), 3,74 (t, J = 6,5 Hz, 2 H), 3,86 (s, 3 H), 4,41 - 4,57 (m, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,97 (d, J = 8,9 Hz, 2 H), 7,25 - 7,36 (m, 4 H), 7,53 (s, 1 H).

Ejemplo 50

Ácido 3-({[4-({ciclohexil[3-etil-1-(4-metoxifenil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico



(1) ciclohexil[3-etil-1-(4-metoxifenil)-1H-pirazol-4-il]metanol

Usando 3-etil-1-(4-metoxifenil)-1H-pirazol-4-carbaldehído (2,1 g) sintetizado en el Ejemplo 48(2) y de la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (1,9 g, 65%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,82 - 2,18 (m., 12H), 2,66 (q, J = 7,6 Hz, 2 H), 3,86 (s, 3 H), 4,34 (dd, J = 8,2, 3,7 Hz, 1 H), 6,97 (d, J = 9,0 Hz, 2 H), 7,32 (d, J = 9,0 Hz, 2 H), 7,57 (s, 1 H).

(2) ácido 3-({[4-({ciclohexil[3-etil-1-(4-metoxifenil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico

Usando ciclohexil[3-etil-1-(4-metoxifenil)-1H-pirazol-4-il]metanol (0,5 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,38 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,35 mg, 43%) en forma de un sólido blanco.

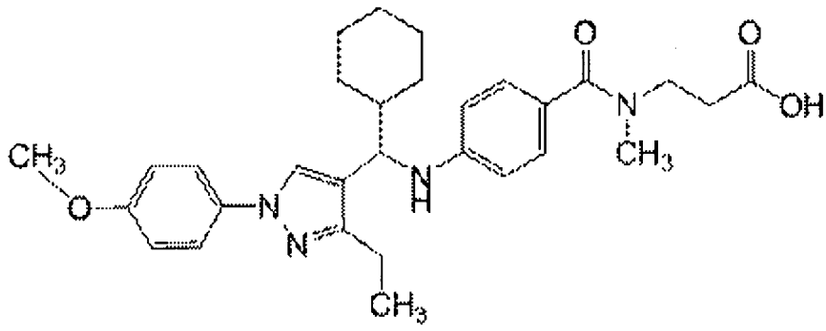
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 (t, J = 7,5 Hz, 3 H), 1,02 - 2,07 (m, 11 H), 2,64 (t, J = 7,3 Hz, 4 H), 3,58 - 3,74 (m, 2 H), 3,84 (s, 3 H), 4,20 (d, J = 7,0 Hz, 1 H), 6,54 (d, J =

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8,7 Hz, 2 H), 6,61 - 6,72 (m, 1 H), 6,95 (d, J = 9,0 Hz, 2 H), 7,25 - 7,55 (m, 5 H).

Ejemplo 51

Ácido 3-[{[4-({ciclohexil[3-etil-1-(4-metoxifenil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



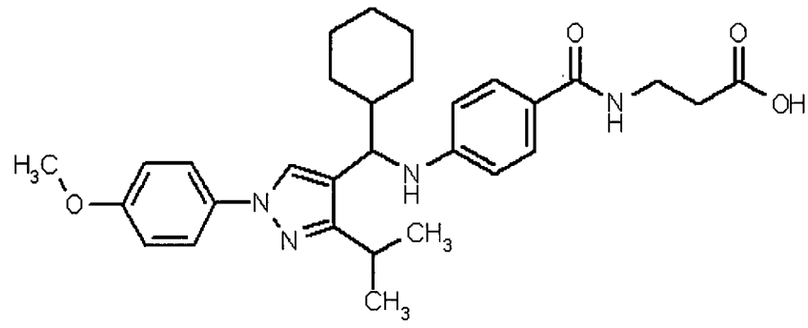
Usando ciclohexil[3-etil-1-(4-metoxifenil)-1H-pirazol-4-il]metanol (0,5 g) sintetizado en el Ejemplo 50(1) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,40 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,15 mg, 18%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 (t, J = 7,5 Hz, 3 H), 1,01 - 2,11 (m, 12 H), 2,56 - 2,83 (m, 4 H), 3,09 (s, 3 H), 3,73 (t, J = 6,4 Hz, 2 H), 3,85 (s, 3 H), 4,19 (d, J = 6,8 Hz, 1 H), 6,54 (d, J = 8,7 Hz, 2 H), 6,96 (d, J = 8,9 Hz, 2 H), 7,27 - 7,37 (m, 4 H), 7,48 (s, 1 H).

Ejemplo 52

Ácido 3-({[4-({ciclohexil[1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico

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(1) 1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-carboxilato de metilo

Usando 4-metil-3-oxopentanoato de metilo (3,6 g), dimetilformamida dimetilacetal (3,5 mL) y monoclorhidrato de p-metoxifenilhidrazina (4,5 g) y de la misma manera que en el Ejemplo 15(1), se obtuvo el compuesto objeto del título (3,5 g, 51%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,37 (d, J = 6,0 Hz, 6 H), 3,20 - 3,40 (m, 1 H), 3,86 (s, 3 H), 3,90 (s, 3 H), 6,98 (d, J = 9,0 Hz, 2 H), 7,27 (d, J = 9,0 Hz, 2 H), 7,29 (s, 1 H), 7,99 (s, 1 H).

(2) 1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-carbaldehído

Usando 1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-carboxilato de metilo (3,5 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(5), se obtuvo el compuesto objeto del título (2,6 g, 84%) en forma de un sólido amarillo pálido.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,37 (d, J = 7,0 Hz, 6 H), 3,12 - 3,25 (m, 1 H), 3,88 (s, 3 H), 7,01 (d, J = 9,0 Hz, 2 H), 7,29 (d, J = 9,0 Hz, 2 H), 8,05 (s, 1 H), 10,06 (s, 1 H).

(3) ciclohexil[1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-il]metanol

Usando 1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-carbaldehído (1,3 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (1,4 g, 84%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,81 - 2,21 (m., 18 H), 3,08 (quint, J = 7,2 Hz, 1 H), 3,86 (s, 3 H), 4,52 (dd, J = 8,7, 3,8 Hz, 1 H), 6,96 (d, J = 9,0 Hz, 2 H), 7,27 (d, J = 9,0 Hz, 2 H), 7,59 (s, 1 H).

(4) ácido 3-({[4-({ciclohexil[1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico

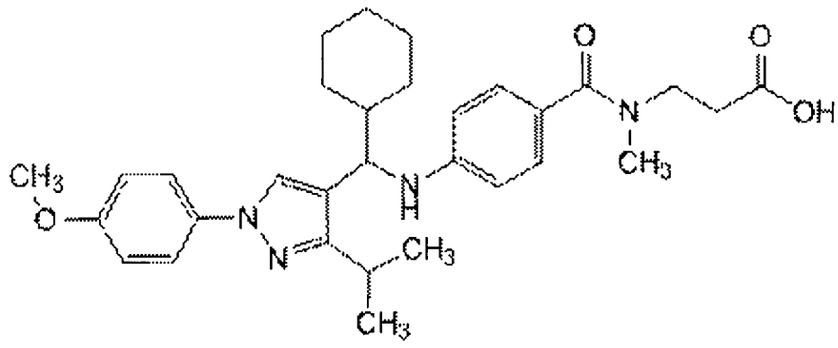
Usando ciclohexil[1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-il]metanol (0,70 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,52 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,34 g, 30%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,10 (d, J = 7,2 Hz, 3 H), 1,18 (d, J = 7,2 Hz, 3 H), 1,20 - 2,06 (m, 12 H), 2,64 (t, J = 5,5 Hz, 2 H), 3,10 (quint, J = 7,3 Hz, 1 H), 3,66 (q, J = 5,8 Hz, 2 H), 3,85 (s, 3 H), 4,37 (d, J = 7,2 Hz, 1 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,61 - 6,74 (m, 1 H), 6,94 (d, J = 8,7 Hz, 2 H), 7,20 - 7,58 (m, 5 H).

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Ejemplo 53

Ácido 3-[{[4-({ciclohexil[1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



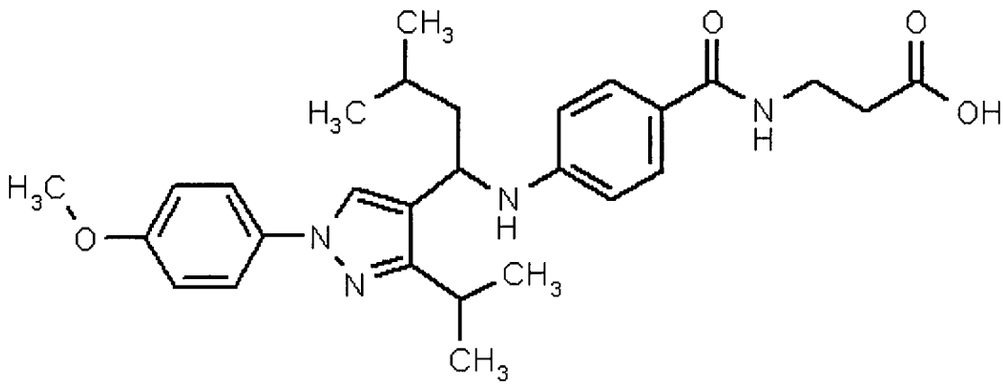
Usando ciclohexil[1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-il]metanol (0,70 g) sintetizado en el Ejemplo 52(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,55 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,28 g, 24%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,11 (d, J = 6,8 Hz, 3 H), 1,19 (d, J = 7,2 Hz, 3 H), 1,20 - 2,13 (m, 11 H), 2,72 (t, J = 6,1 Hz, 2 H), 3,03 - 3,23 (m, 4 H), 3,73 (t, J = 6,6 Hz, 2 H), 3,85 (s, 3 H), 4,36 (d, J = 7,2 Hz, 1 H), 6,55 (d, J = 8,3 Hz, 2 H), 6,95 (d, J = 9,1 Hz, 2 H), 7,21 - 7,35 (m, 4 H), 7,50 (s, 1 H).

Ejemplo 54

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Ácido 3-({[4-({1-[1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-il]-3-metilbutil}amino)fenil]carbonil}amino)propanoico



(1) 1-[1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-il]-3-metilbutan-1-ol

Usando 1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-carbaldehído (1,3 g) sintetizado en el Ejemplo 52(2) y de la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (1,6 g, 98%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,99 (d, J = 5,7 Hz, 6 H), 1,28 (dd, J = 17,0, 7,2 Hz, 6 H), 1,75 - 1,98 (m, 2 H), 2,99 - 3,19 (m, 1 H), 3,86 (s, 3 H), 4,96 (dd, J = 8,4, 4,4 Hz, 1 H), 6,97 (d, J = 8,9 Hz, 2 H), 7,26 (d, J = 9,0 Hz, 2 H), 7,62 (s, 1 H).

(2) ácido 3-({[4-({1-[1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-il]-3-metilbutil}amino)fenil]carbonil}amino)propanoico

Usando 1-[1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-il]-3-metilbutan-1-ol (0,57 g) sintetizado con anterioridad

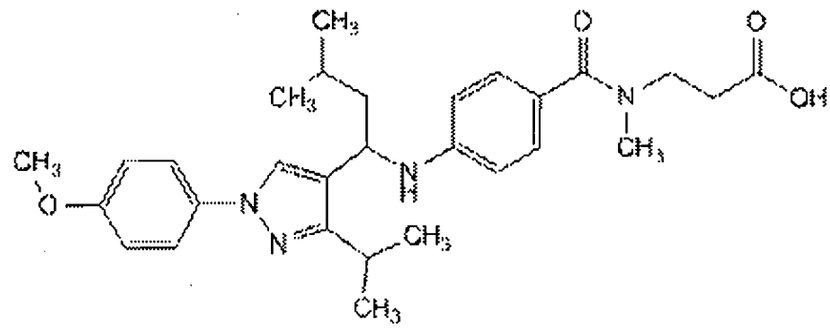
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y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,45 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (28,0 mg, 3%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 (d, J = 6,4 Hz, 3 H), 1,02 (d, J = 6,4 Hz, 3 H), 1,11 - 1,98 (m, 9 H), 2,67 (t, J = 5,7 Hz, 2 H), 2,98 - 3,19 (m, 1 H), 3,68 (t, J = 6,0 Hz, 2 H), 3,85 (s, 3 H), 4,66 (d, J = 9,0 Hz, 1 H), 6,51 - 6,77 (m, 3 H), 6,95 (d, J = 8,9 Hz, 2 H), 7,26 - 7,59 (m, 5 H).

Ejemplo 55

Ácido 3-[{[4-({1-[1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-il]-3-metilbutil}amino)fenil]carbonil}(metil)amino]propanoico



Usando 1-[1-(4-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-il]-3-metilbutan-1-ol (0,57 g) sintetizado en el Ejemplo 54(1) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,48 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (8,0 mg, 1%) en forma de un sólido blanco.

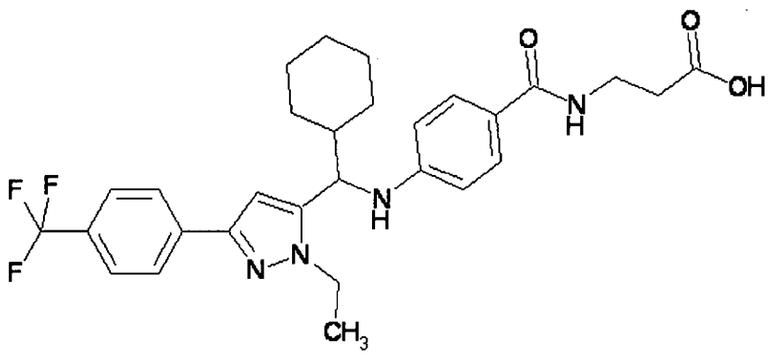
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 (d, J = 6,6 Hz, 3 H), 1,02 (d, J = 6,4 Hz, 3 H), 1,11 - 2,01 (m, 9 H), 2,72 (br. s., J = 6,0 Hz, 2 H), 2,96 - 3,24 (m, 4 H), 3,74 (br. s., J = 6,0 Hz,

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2 H), 3,86 (s, 3 H), 4,63 (d, J = 6,0 Hz, 1 H), 6,50 - 6,70 (m, 2 H), 6,96 (d, J = 8,9 Hz, 2 H), 7,21 - 7,38 (m, 4 H), 7,59 (br. s., 1 H).

Ejemplo 56

Ácido 3-[({4-[(ciclohexil{1-etil-3-[4-(trifluorometil)fenil]-1H-pirazol-5-il}metil)amino]fenil}carbonil)amino]propanoico




(1) 1-etil-3-[4-(trifluorometil)fenil]-1H-pirazol-5-carboxilato de etilo

La 1-[4-(trifluorometil)fenil]etanona (12,0 g) se disolvió en etanol (100 mL), hidruro de sodio (60%, oleoso, 2,8 g) se añadió cuidadosamente bajo enfriamiento con hielo. Después de agitar durante 5 min, se añadió dietiloxalato (8,7 mL) y la mezcla se agitó a temperatura ambiente durante la noche. El precipitado (18,6 g) se recogió y a 7,3 g de ello se añadieron etanol (16 mL), ácido clorhídrico 6 N (4,3 mL) y etilhidrazina (1,6 g) y la mezcla se agitó a temperatura ambiente durante la noche. El solvente se evaporó a presión reducida y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se

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purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (5,7 g, 78%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,42 (t, J = 7,2 Hz, 3 H), 1,50 (t, J = 7,2 Hz, 3 H), 4,39 (q, J = 7,2 Hz, 2 H), 4,66 (q, J = 7,2 Hz, 2 H), 7,17 (s, 1 H), 7,65 (d, J = 8,1 Hz, 2 H), 7,92 (d, J = 8,1 Hz, 2 H).

(2) 1-etil-3-[4-(trifluorometil)fenil]-1H-pirazol-5-carbaldehído

Usando 1-etil-3-[4-(trifluorometil)fenil]-1H-pirazol-5-carboxilato de etilo (5,7 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(5), se obtuvo el compuesto objeto del título (3,2 g, 68%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,48 (t, J = 7,2 Hz, 3 H), 4,25 (q, J = 7,2 Hz, 2 H), 6,85 (s, 1 H), 7,54 (d, J = 8,0 Hz, 2 H), 7,77 (d, J = 8,0 Hz, 2 H), 10,01 (s, 1 H).

(3) ciclohexil{1-etil-3-[4-(trifluorometil)fenil]-1H-pirazol-5-il}metanol

Usando el 1-etil-3-[4-(trifluorometil)fenil]-1H-pirazol-5-carbaldehído (2,28 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (1,2 g, 41%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 2,00 (m, 11 H), 1,39 (t, J = 7,2 Hz, 3 H), 2,27 (d, J = 4,7 Hz, 1 H), 4,00 - 4,25 (m, 2 H), 4,53 (dd, J = 6,4, 4,7 Hz, 1 H), 6,23 (s, 1 H), 7,53 (d, J = 7,9 Hz, 2 H), 7,72 (d, J = 7,9 Hz, 2 H).

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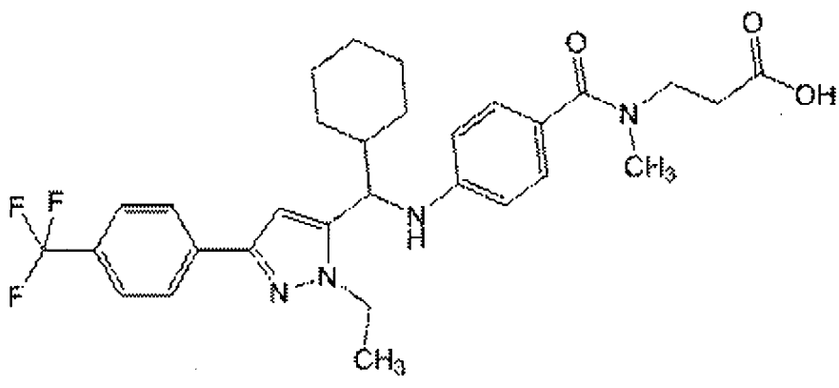
(4) ácido 3-[({4-[(ciclohexil{1-etil-3-[4-(trifluorometil)fenil]-1H-pirazol-5-il}metil)amino]fenil}carbonil)amino]propanoico

Usando ciclohexil{1-etil-3-[4-(trifluorometil)fenil]-1H-pirazol-5-il}metanol (0,6 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,42 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,18 g, 20%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 - 1,27 (m, 11 H), 1,33 (t, J = 7,3 Hz, 3 H), 2,68 (t, J = 5,5 Hz, 2 H), 3,59 - 3,80 (m, 2 H), 4,11 (q, J = 7,2 Hz, 2 H), 4,39 (d, J = 6,8 Hz, 1 H), 6,16 (s, 1 H), 6,64 (d, J = 8,7 Hz, 2 H), 6,70 - 6,83 (m, 1 H), 7,48 (d, J = 8,1 Hz, 2 H), 7,58 (d, J = 8,7 Hz, 2 H), 7,69 (d, J = 8,1 Hz, 2 H).

Ejemplo 57

Ácido 3-[({4-[(ciclohexil{1-etil-3-[4-(trifluorometil)fenil]-1H-pirazol-5-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



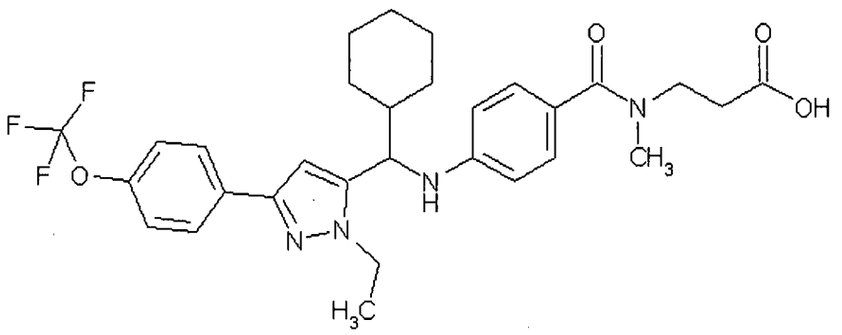
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Usando ciclohexil{1-etil-3-[4-(trifluorometil)fenil]-1H-pirazol-5-il}metanol (0,6 g) sintetizado en el Ejemplo 56(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,48 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,19 g, 19%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 2,00 (m, 11 H), 1,35 (t, J = 7,2 Hz, 3 H), 2,62 - 2,78 (m, 2 H), 3,09 (s, 3 H), 3,75 (t, J = 6,6 Hz, 2 H), 4,15 (q, J = 7,2 Hz, 2 H), 4,39 (d, J = 6,6 Hz, 1 H), 6,18 (s, 1 H), 6,61 (d, J = 8,7 Hz, 2 H), 7,25 (d, J = 8,7 Hz, 2 H), 7,50 (d, J = 8,1 Hz, 2 H), 7,70 (d, J = 8,1 Hz, 2 H).

Ejemplo 58

Ácido 3-[({4-[(ciclohexil{1-etil-3-[4-(trifluorometoxi)fenil]-1H-pirazol-5-il}metil)amino]fenil}carbonil)(metil)amino]propanoico




(1) 1-etil-3-[4-(trifluorometoxi)fenil]-1H-pirazol-5-carboxilato de etilo

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Usando 1-[4-(trifluorometoxi)fenil]etanona (13,0 g), hidruro de sodio (60%, oleoso, 2,8 g), dietiloxalato (8,7 mL) y etilhidrazina (4,2 g) y de la misma manera que en el Ejemplo 56(1), se obtuvo el compuesto objeto del título (19,4 g, 92%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,34 - 1,53 (m, 6 H), 4,24 (d, J = 7,2 Hz, 2 H), 4,23 (q, J = 7,2 Hz, 2 H), 4,43 (q, J = 7,2 Hz, 2 H), 4,45 (d, J = 7,2 Hz, 2 H), 6,82 (s, 1 H), 7,33 (d, J = 9,0 Hz, 2 H), 7,44 (d, J = 9,0 Hz, 2 H).

(2) 1-etil-3-[4-(trifluorometoxi)fenil]-1H-pirazol-5-carbaldehído

Usando 1-etil-3-[4-(trifluorometoxi)fenil]-1H-pirazol-5-carboxilato de etilo (5,0 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(5), se obtuvo el compuesto objeto del título (4,9 g, 38%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,48 (t, J = 7,3 Hz, 3 H), 4,23 (q, J = 7,3 Hz, 2 H), 6,80 (s, 1 H), 7,30 - 7,58 (m, 4 H), 10,00 (s, 1 H).

(3) ciclohexil{1-etil-3-[4-(trifluorometoxi)fenil]-1H-pirazol-5-il}metanol

Usando 1-etil-3-[4-(trifluorometoxi)fenil]-1H-pirazol-5-carbaldehído (2,5 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (1,7 g, 54%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,26 -2,00 (m, 11 H), 1,39 (t, J = 7,2 Hz, 3 H), 4,12 (d, J = 7,2 Hz, 2 H), 4,52 (d, J = 6,4

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Hz, 1 H), 6,18 (s, 1 H), 7,30 (d, J = 8,7 Hz, 2 H), 7,43 (d, J = 8,7 Hz, 2 H).

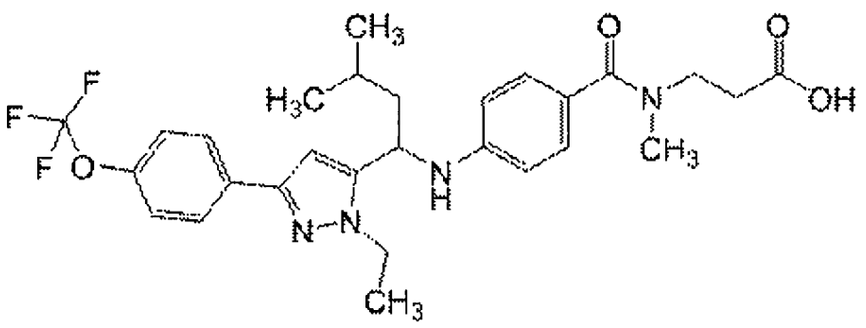
(4) ácido 3-[({4-[(ciclohexil{1-etil-3-[4-(trifluorometoxi)fenil]-1H-pirazol-5-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

Usando ciclohexil{1-etil-3-[4-(trifluorometoxi)fenil]-1H-pirazol-5-il}metanol (0,39 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,32 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,06 g, 11%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,99 - 2,00 (m, 11 H), 1,36 (t, J = 7,2 Hz, 3 H), 2,74 (t, J = 6,2 Hz, 2 H), 3,10 (s, 3 H), 3,74 (t, J = 6,2 Hz, 2 H), 4,12 (q, J = 7,2 Hz, 2 H), 4,37 (d, J = 6,4 Hz, 1 H), 6,10 (s, 1 H), 6,63 (d, J = 8,7 Hz, 2 H), 7,26 - 7,46 (m, 6 H).

Ejemplo 59

Ácido 3-[({4-[(1-{1-etil-3-[4-(trifluorometoxi)fenil]-1H-pirazol-5-il}-3-metilbutil)amino]fenil}carbonil)(metil)amino]propanoico



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(1) 1-{1-etil-3-[4-(trifluorometoxi)fenil]-1H-pirazol-5-il}-3-metilbutan-1-ol

1-Etil-3-[4-(trifluorometoxi)fenil]-1H-pirazol-5-carbaldehído (2,5 g) sintetizado en el Ejemplo 58(2) se disolvió en tetrahidrofurano (20 mL) y se añadió solución 1 M de bromuro de isobutilmagnesio - tetrahidrofurano (12 mL) gota a gota a 0 °C. De la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (0,9 g, 31%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 (d, J = 6,4 Hz, 6 H), 1,39 (t, J = 7,2 Hz, 3 H), 1,56 - 1,98 (m, 3 H), 2,21 (d, J = 4,3 Hz, 1 H), 4,10 - 4,30 (q, J = 7,2 Hz, 2 H), 4,86 (ddd, J = 8,9, 4,7, 4,3 Hz, 1 H), 6,22 (s, 1 H), 7,32 - 7,50 (m, 4 H).

(2) ácido 3-[({4-[(1-{1-etil-3-[4-(trifluorometoxi)fenil]-1H-pirazol-5-il}-3-metilbutil)amino]fenil}carbonil)(metil)amino]propanoico

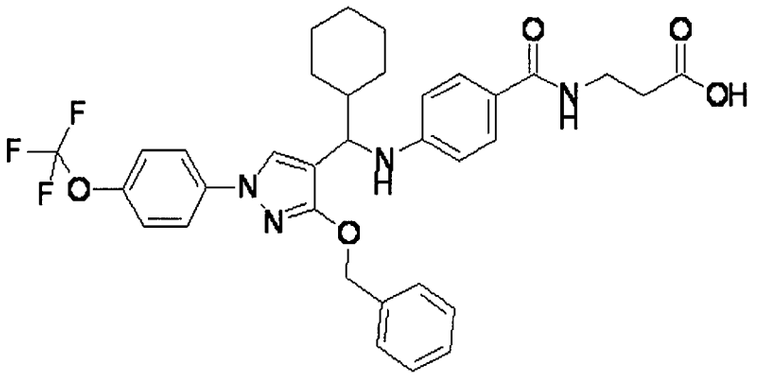
Usando ciclohexil1-{1-etil-3-[4-(trifluorometoxi)fenil]-1H-pirazol-5-il}-3-metilbutan-1-ol (0,39 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,28 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,02 g, 4%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 (dd, J = 19,1, 6,2 Hz, 6 H), 1,34 (t, J = 7,2 Hz, 3 H), 1,55 - 1,97 (m, 3 H), 2,70 (br. s., 2 H), 3,07 (s, 3 H), 3,73 (br. s., 2 H), 4,10 (q, J = 7,2 Hz, 2 H), 4,61 (t, J = 6,8 Hz, 1 H), 6,17 (s, 1 H), 6,67 (d, J = 8,0 Hz, 2 H), 7,34 - 7,49 (m, 6 H).

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Ejemplo 60

Ácido 3-{[(4-{[{3-(benciloxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico



(1) 3-(benciloxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carbaldehído

Usando 3-(benciloxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carboxilato de etilo (3,1 g) sintetizado en el método descrito en el documento EP1394154 y de la misma manera que en el Ejemplo 1(5), se obtuvo el compuesto objeto del título (2,1 g, 75%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 5,50 (s, 2 H), 7,27 - 7,70 (m, 9 H), 8,24 (s, 1 H), 10,00 (s, 1 H).

(2) {3-(benciloxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}(ciclohexil)metanol

Usando 3-(benciloxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carbaldehído (2,1 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (1,9 g, 76%) en forma de un sólido blanco.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 2,00 (m, 12 H), 4,44 (dd, J = 6,8, 5,3 Hz, 1 H), 5,36 (s, 2 H), 7,26 - 7,51 (m, 9 H), 7,66 (s, 1 H).

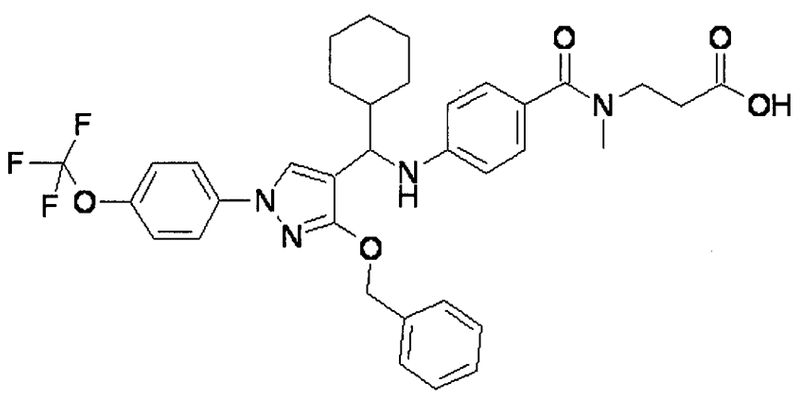
(3) ácido 3-{[(4-{[{3-(benciloxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico

Usando {3-(benciloxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}(ciclohexil)metanol (0,50 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,26 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,39 g, 56%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,78 - 2,00 (m, 11 H), 2,12 - 2,42 (m, 2 H), 3,30 - 3,57 (m, 2 H), 4,14 (d, J = 7,0 Hz, 1 H), 5,31 (s, 2 H), 6,41 (d, J = 8,5 Hz, 2 H), 6,77 (br. s., 1 H), 7,12 (d, J = 9,0 Hz, 2 H), 7,29 - 7,67 (m, 10 H).

Ejemplo 61

Ácido 3-{[(4-{[{3-(benciloxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico



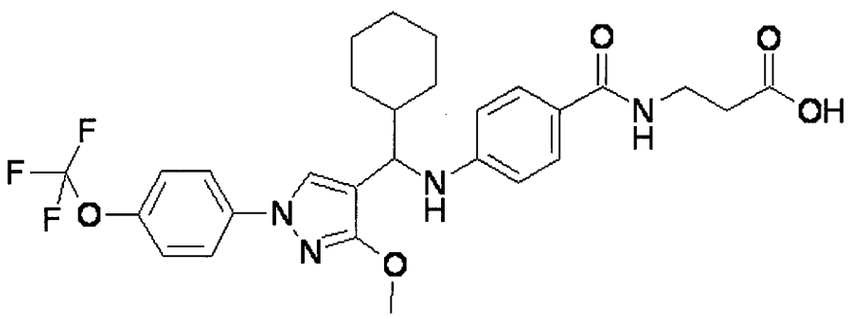
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Usando {3-(benciloxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}(ciclohexil)metanol (0,50 g) sintetizado en el Ejemplo 60(2) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,28 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,37 g, 52%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,87 - 2,05 (m, 11 H), 2,52 (t, J = 6,0 Hz, 2 H), 2,96 (s, 3 H), 3,50 - 3,78 (m, 2 H), 4,20 (d, J = 6,8 Hz, 1 H), 5,25 - 5,46 (m, 2 H), 6,47 (d, J = 8,7 Hz, 2 H), 7,12 - 7,62 (m, 12 H).

Ejemplo 62

Ácido 3-[({4-[(ciclohexil{3-metoxi-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico




(1) 3-metoxi-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carbaldehído

Usando 3-metoxi-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carboxilato de etilo (4,8 g) sintetizado en el método

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descrito en el documento WO 2007/89031 y de la misma manera que en el Ejemplo 1(5), se obtuvo el compuesto objeto del título (1,0 g, 35%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 4,10 (s, 3 H), 7,33 (d, J = 9,1 Hz, 2 H), 7,69 (d, J = 9,1 Hz, 2 H), 8,23 (s, 1 H), 9,87 (s, 1 H).

(2) ciclohexil{3-metoxi-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metanol

Usando 3-metoxi-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carbaldehído (1,0 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (1,5 g, 75%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 2,02 (m, 11 H), 3,62 (br. s., 1 H), 4,00 (s, 3 H), 4,40 (dd, J = 7,0, 4,7 Hz, 1 H), 7,24 - 7,62 (m, 4 H), 7,64 (s, 1 H).

(3) 3-metoxi-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carboxilato de etilo

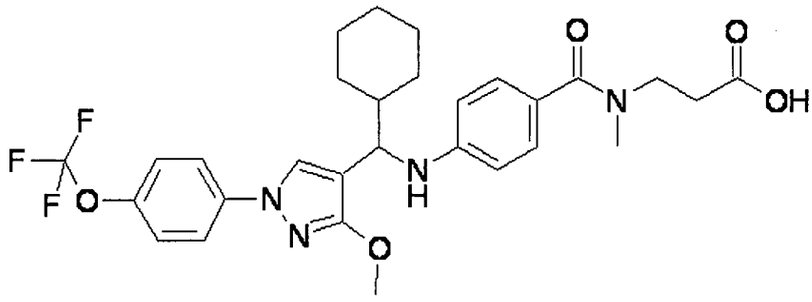
Usando ciclohexil{3-metoxi-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metanol (0,75 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,47 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,10 g, 9%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,88 - 2,00 (m, 11 H), 2,58 (t., J = 6,0 Hz, 2 H), 3,54 - 3,68 (m, 2 H), 4,00 (s, 3 H), 4,20 (d, J = 6,6 Hz, 1 H), 6,52 (d, J = 8,7 Hz, 2 H), 6,56 - 6,68 (m, 1 H), 7,20 (d, J = 8,3 Hz, 2 H), 7,48 - 7,59 (m, 5 H).

Ejemplo 63

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Ácido 3-[({4-[(ciclohexil{3-metoxi-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



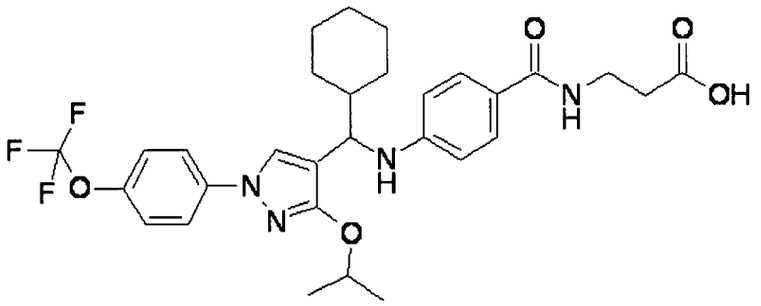
Usando ciclohexil{3-metoxi-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metanol (0,75 g) sintetizado en el Ejemplo 62(2) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,50 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,13 g, 12%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 2,02 (m, 11 H), 2,68 (t, J = 6,2 Hz, 2 H), 3,05 (s, 3 H), 3,71 (t, J = 6,4 Hz, 2 H), 4,01 (s, 3 H), 4,19 (d, J = 6,6 Hz, 1 H), 6,53 (d, J = 8,7 Hz, 2 H), 7,17 - 7,28 (m, 4 H), 7,47 - 7,61 (m, 3 H).

Ejemplo 64

Ácido 3-[({4-[(ciclohexil{3-(1-metiletoxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

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(1) 3-(1-metiletoxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carbaldehído

Usando 3-(1-metiletoxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carboxilato de etilo (1,3 g) sintetizado en el método descrito en el documento WO 2007/89031 y de la misma manera que en el Ejemplo 1(5), se obtuvo el compuesto objeto del título (0,43 g, 37%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,33 (d, J = 6,2 Hz, 6 H), 5,20 (quint, J = 6,2 Hz, 1 H), 7,03 - 7,76 (m, 4 H), 7,98 (s, 1 H), 9,78 (s, 1 H).

(2) ciclohexil{3-(1-metiletoxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metanol

Usando 3-(1-metiletoxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-carbaldehído (0,43 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (0,40 g, 74%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,47 - 2,20 (m, 17 H), 3,61 (br, s. 1 H), 4,20 - 4,40 (m, 2 H), 7,28 (d, J = 8,7 Hz, 2 H), 7,57 (s, 1 H), 7,74 (d, J = 8,7 Hz, 2 H).

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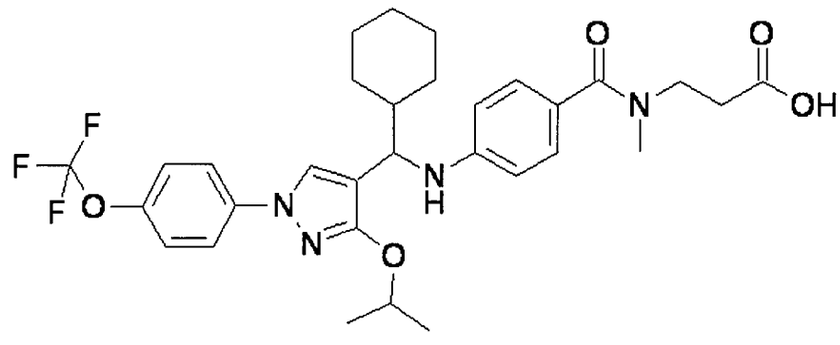
(3) ácido 3-[({4-[(ciclohexil{3-(1-metiletoxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico

Usando ciclohexil{3-(1-metiletoxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metanol (0,20 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,12 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,11 g, 36%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 2,08 (m, 11 H), 1,11 - 1,18 (m, 6 H), 2,50 - 2,66 (m, 2 H), 3,54 - 3,70 (m, 2 H), 4,11 - 4,30 (m, 2 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,69 (br. s., 1 H), 7,26 (d, J = 8,7 Hz, 2 H), 7,46 (s, 1 H), 7,57 (d, J = 8,7 Hz, 2 H).

Ejemplo 65

Ácido 3-[({4-[(ciclohexil{3-(1-metiletoxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



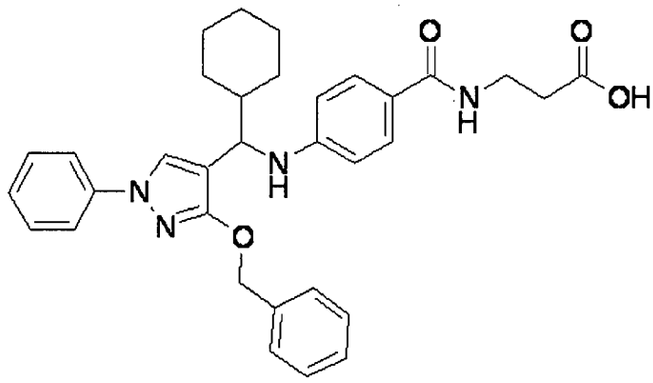
1072

Usando ciclohexil{3-(1-metiletoxi)-1-[4-(trifluorometoxi)fenil]-1H-pirazol-4-il}metanol (0,20 g) sintetizado en el Ejemplo 64(2) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,13 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,11 g, 36%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 - 2,00 (m, 11 H), 1,12 - 1,19 (m, 6 H), 2,53 - 2,70 (m, 2 H), 3,05 (s, 3 H), 3,63 - 3,78 (m, 2 H), 4,13 - 4,29 (m, 2 H), 6,57 (d, J = 8,9 Hz, 2 H), 7,27 - 7,32 (m, 4 H), 7,46 (s, 1 H), 7,72 (d, J = 8,9 Hz, 2 H).

Ejemplo 66

Ácido 3-({[4-({[3-(benciloxi)-1-fenil-1H-pirazol-4-il](ciclohexil)metil}amino)fenil]carbonil}amino)propanoico



(1) 3-(benciloxi)-1-fenil-1H-pirazol-4-carbaldehído

Usando 3-(benciloxi)-1-fenil-1H-pirazol-4-carboxilato de etilo (1,8 g) sintetizado en el método descrito en el documento EP1394154 y de la misma manera que en el Ejemplo

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1(5), se obtuvo el compuesto objeto del título (1,4 g, 90%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 5,50 (s, 2 H), 7,29 - 7,78 (m, 10 H), 8,26 (s, 1 H), 9,98 (s, 1 H).

(2) [3-(benciloxi)-1-fenil-1H-pirazol-4-il](ciclohexil)metanol

Usando 3-(benciloxi)-1-fenil-1H-pirazol-4-carbaldehído (1,4 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo 1(6), se obtuvo el compuesto objeto del título (1,6 g, 91%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,58 - 2,20 (m, 12 H), 4,44 (dd, J = 7,2, 5,3 Hz, 1 H), 5,37 (s, 2 H), 7,10 - 7,62 (m, 10 H), 7,69 (s, 1 H).

(3) Ácido 3-({[4-({[3-(benciloxi)-1-fenil-1H-pirazol-4-il](ciclohexil)metil}amino)fenil]carbonil}amino)propanoico

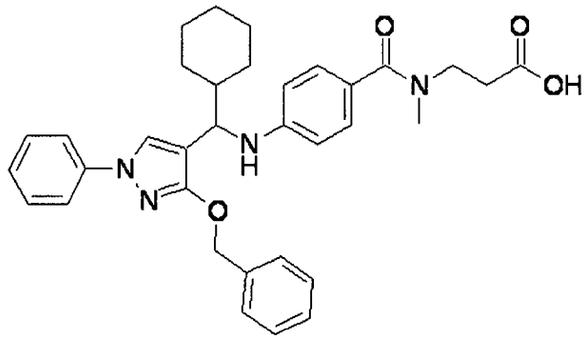
Usando [3-(benciloxi)-1-fenil-1H-pirazol-4-il](ciclohexil)metanol (0,79 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,51 g) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,51 g, 43%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 - 1,97 (m, 11 H), 2,30 - 2,48 (m, 2 H), 3,37 - 3,58 (m, 2 H), 4,18 (d, J = 6,6 Hz, 1 H), 5,24 - 5,42 (m, 2 H), 6,44 (d, J = 8,7 Hz, 2 H), 6,66 (br. s., 1 H), 7,02 - 7,63 (m, 13 H).

Ejemplo 67

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Ácido 3-[{[4-({[3-(benciloxi)-1-fenil-1H-pirazol-4-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoico



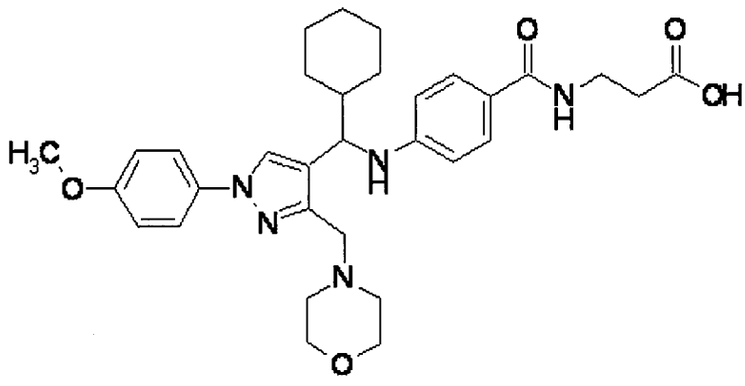
Usando [3-(benciloxi)-1-fenil-1H-pirazol-4-il](ciclohexil)metanol (0,79 g) sintetizado en el Ejemplo 66(2) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 1(7), se obtuvo el compuesto objeto del título (0,68 g, 55%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 - 2,01 (m, 11 H), 2,71 (d, J = 6,0 Hz, 1 H), 3,06 (s, 3 H), 3,71 (t, J = 6,4 Hz, 2 H), 4,23 (d, J = 6,6 Hz, 1 H), 5,28 - 5,47 (m, 2 H), 6,50 (d, J = 8,7 Hz, 2 H), 7,10 - 7,64 (m, 13 H).

Ejemplo 68

Ácido 3-({[4-({ciclohexil[1-(4-metoxifenil)-3-(morfolin-4-ilmetil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico

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(1) 4-(morfolin-4-il)-3-oxobutanoato de metilo

A una solución (300 mL) de 4-cloro-3-oxobutanoato de metilo (27,1 g) en tetrahidrofurano se añadió morfolina (34,5 g) bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 2 h. El solvente se evaporó a presión reducida, se añadió ácido clorhídrico 1 N (100 mL) y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:10, relación en volumen) para dar el compuesto objeto del título (12,8 g, 35%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,37 - 2,55 (m, 4 H), 3,26 (s, 2 H), 3,52 (s, 2 H), 3,70 - 3,76 (m, 4 H), 3,74 (s, 3 H).

(2) 1-(4-metoxifenil)-3-(morfolin-4-ilmetil)-1H-pirazol-4-carboxilato de metilo

Al 4-(morfolin-4-il)-3-oxobutanoato de metilo (7,0 g) mencionado en el punto (1) se añadió dimetilformamida-dimetilacetal (4,9 mL) y la mezcla se agitó a 100 °C durante

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2 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, se añadieron etanol (200 mL) y clorhidrato de 4-metoxifenilhidrazina (6,3 g) y la mezcla se agitó a 100 °C durante 3 h. La mezcla se dejó enfriar hasta temperatura ambiente y el solvente se evaporó a presión reducida. Se añadió agua al residuo y la mezcla se extrajo con acetato de etilo. El extracto se concentró y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (10,6 g, 93%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,44 - 2,50 (m, 4 H), 3,60 - 3,65 (m, 4 H), 3,75 (s, 2 H), 3,86 (s, 3 H), 3,87 (s, 3 H), 6,97 (d, J = 9,1 Hz, 2 H), 7,68 (d, J = 9,1 Hz, 2 H), 8,03 (s, 1 H).

(3) 1-(4-metoxifenil)-3-(morfolin-4-ilmetil)-1H-pirazol-4-carbaldehído

Una solución (20 mL) de 1-(4-metoxifenil)-3-(morfolin-4-ilmetil)-1H-pirazol-4-carboxilato de metilo (11,3 g) sintetizada en el punto (2) antes mencionado en tetrahidrofurano se añadió a una solución helada (80 mL) de hidruro de litio y aluminio (1,4 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla se enfrió con hielo nuevamente y se añadieron sucesivamente agua (3,7 mL), solución acuosa 1 N de hidróxido de sodio (18,5 mL) y agua (3,7 mL) gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a

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presión reducida para dar un producto crudo (8,5 g) de 1-(4-metoxifenil)-3-(morfolin-4-ilmetil)-1H-pirazol-4-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (150 mL), se añadió dióxido de manganeso (15 g) y la mezcla se calentó durante 30 min con una trampa de Dean-Stark. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y el dióxido de manganeso se recogió por filtración. El solvente se evaporó a presión reducida para dar el compuesto objeto del título (7,2 g, 70%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,44 - 2,50 (m, 4 H), 3,60 - 3,65 (m, 4 H), 3,72 (s, 2 H), 3,88 (s, 3 H), 6,99 (d, J = 9,1 Hz, 2 H), 7,60 (d, J = 9,1 Hz, 2 H), 8,08 (s, 1 H), 10,10 (s, 1 H).

(4) ciclohexil[1-(4-metoxifenil)-3-(morfolin-4-ilmetil)-1H-pirazol-4-il]metanol

A una solución (15 mL) de 1-(4-metoxifenil)-3-(morfolin-4-ilmetil)-1H-pirazol-4-carbaldehído (2,0 g) sintetizada en el punto (3) antes mencionado en tetrahidrofurano se añadió gota a gota bromuro de ciclohexilmagnesio (10 mL, solución 1 M de tetrahidrofurano) bajo enfriamiento con hielo. Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen)

para dar el compuesto objeto del título (1,3 g, 51%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 2,20 (m, 11 H), 2,24 - 2,50 (m, 4 H), 3,47 (d, J = 12,0 Hz, 1 H), 3,58 - 3,73 (m, 5 H), 3,87 (s, 3 H), 4,43 (d, J = 6,6 Hz, 1 H), 6,10 (s, 1 H), 6,98 (d, J = 8,9 Hz, 2 H), 7,26 (d, J = 8,9 Hz, 2 H), 7,49 (s, 1 H).

(5) ácido 3-({[4-({ciclohexil[1-(4-metoxifenil)-3-(morfolin-4-ilmetil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico

A una solución (15 mL) de ciclohexil[1-(4-metoxifenil)-3-(morfolin-4-ilmetil)-1H-pirazol-4-il]metanol (0,65 g) sintetizada en el punto (4) antes mencionado en tetrahidrofurano se añadió cloruro de tionilo (0,37 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y se añadió cuidadosamente solución saturada acuosa de carbonato ácido de sodio (15 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (15 mL), se añadieron yoduro de sodio (0,37 g), carbonato de sodio (0,27 g) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,39 g) sintetizado en el Ejemplo 1(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el

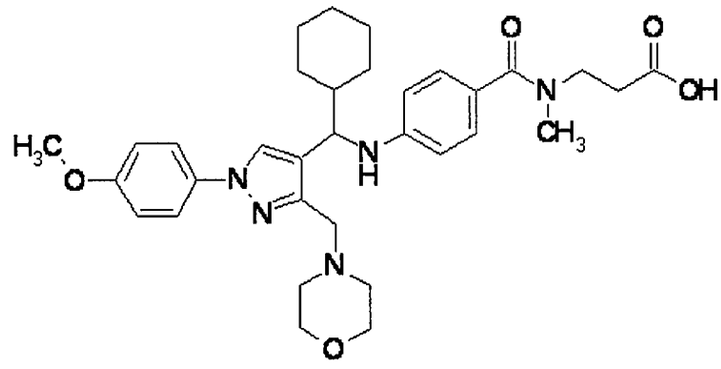
residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-({[4-({ciclohexil[1-(4-metoxifenil)-3-(morfolin-4-ilmetil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoato de etilo (0,35 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (2 mL), se añadió solución acuosa 1 N de hidróxido de sodio (1,5 mL) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,5 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,22 g, 22%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 2,00 (m, 11 H), 2,24 - 2,50 (m, 4 H), 2,66 (br s., 2 H), 3,44 (s, 2 H), 3,58 - 3,73 (m, 6 H), 3,85 (s, 3 H), 4,47 (d, J = 7,2 Hz, 1 H), 6,47 - 6,79 (m, 3 H), 6,94 (d, J = 8,7 Hz, 2 H), 7,26 - 7,30 (m, 2 H), 7,50 - 7,60 (m, 3 H).

Ejemplo 69

Ácido 3-[{[4-({ciclohexil[1-(4-metoxifenil)-3-(morfolin-4-ilmetil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

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A una solución (15 mL) de ciclohexil[1-(4-metoxifenil)-3-(morfolin-4-ilmetil)-1H-pirazol-4-il]metanol (0,65 g) sintetizado en el Ejemplo 68(4) en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,37 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y se vertió cuidadosamente solución saturada acuosa de carbonato ácido de sodio (15 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (15 mL), se añadieron yoduro de sodio (0,37 g), carbonato de sodio (0,27 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,42 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[1-(4-metoxifenil)-3-(morfolin-4-ilmetil)-

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1H-pirazol-4-

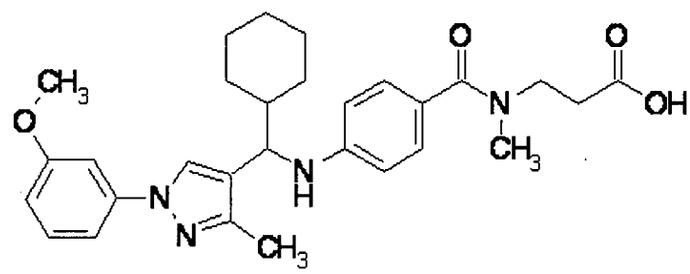
il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,38 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (2 mL), se añadió solución acuosa 1 N de hidróxido de sodio (1,0 mL) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y el ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,12 g, 12%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,89 - 2,10 (m, 11 H), 2,50 - 2,75 (m, 6 H), 3,07 (s, 3 H), 3,50 - 3,85 (m, 6 H), 3,88 (s, 3 H), 4,17 - 4,25 (m, 2 H), 4,70 - 4,78 (m, 1 H), 6,83 (d, J = 8,7 Hz, 2 H), 7,02 (d, J = 9,0 Hz, 2 H), 7,19 - 7,35 (m, 4 H), 7,77 (s, 1 H).

Ejemplo 70

Ácido 3-[{[4-({ciclohexil[1-(3-metoxifenil)-3-metil-1H-pirazol-4-

il]metil}amino)fenil]carbonil}(metil)amino]propanoico



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(1) 1-(3-metoxifenil)-3-metil-1H-pirazol-4-carboxilato de metilo

El 3-metil-1H-pirazol-4-carboxilato de metilo (4,6 g) sintetizado en el Ejemplo 1(3) se disolvió en N,N-dimetilacetamida (50 mL), se añadieron ácido 3-metoxifenilborónico (10,0 g), acetato de cobre (12,0 g) y piridina (10,6 mL) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite, se añadió ácido clorhídrico 1 N (100 mL) al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (3,9 g, 48%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,56 (s, 3 H), 3,86 (s, 3 H), 3,87 (s, 3 H), 6,80 - 8,33 (m, 5 H).

(2) 1-(3-metoxifenil)-3-metil-1H-pirazol-4-carbaldehído

Una solución (20 mL) de 1-(3-metoxifenil)-3-metil-1H-pirazol-4-carboxilato de metilo (3,9 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (80 mL) de hidruro de litio y aluminio (0,6 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla se enfrió con hielo nuevamente y se añadieron sucesivamente agua (1,6 mL), solución acuosa 1 N de hidróxido de sodio (7,8 mL) y agua (1,6 mL) gota a gota para

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neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar un producto crudo (1,9 g) de 1-(3-metoxifenil)-3-metil-1H-pirazol-4-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (30 mL), se añadió dióxido de manganeso (3,0 g) y la mezcla se calentó durante 30 min con una trampa de Dean-Stark. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y dióxido de manganeso se recogió por filtración. El solvente se evaporó a presión reducida para dar el compuesto objeto del título (1,2 g, 64%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,59 (s, 3 H), 3,88 (s, 3 H), 6,80 - 7,40 (m, 4 H), 8,32 (s, 1 H), 10,00 (s, 1 H).

(3) ciclohexil[1-(3-metoxifenil)-3-metil-1H-pirazol-4-il]metanol

A una solución (15 mL) de 1-(3-metoxifenil)-3-metil-1H-pirazol-4-carbaldehído (0,62 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano bajo enfriamiento con hielo se añadió gota a gota bromuro de ciclohexilmagnesio (4,3 mL, solución 1 M de tetrahidrofurano). Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar

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el compuesto objeto del título (0,60 g, 70%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 2,10 (m, 12 H), 2,34 (s, 3 H), 3,87 (s, 3 H), 4,43 (d, J = 7,2 Hz, 1 H), 6,70 - 7,40 (m, 4 H), 7,78 (s, 1 H).

(4) ácido 3-[{[4-({ciclohexil[1-(3-metoxifenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (3 mL) de ciclohexil[1-(3-metoxifenil)-3-metil-1H-pirazol-4-il]metanol (0,30 g) sintetizada en el punto (3) antes mencionado en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,11 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y se vertió cuidadosamente una solución saturada acuosa de carbonato ácido de sodio (5 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (5 mL), se añadieron yoduro de sodio (0,23 g), carbonato de sodio (0,16 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,25 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice

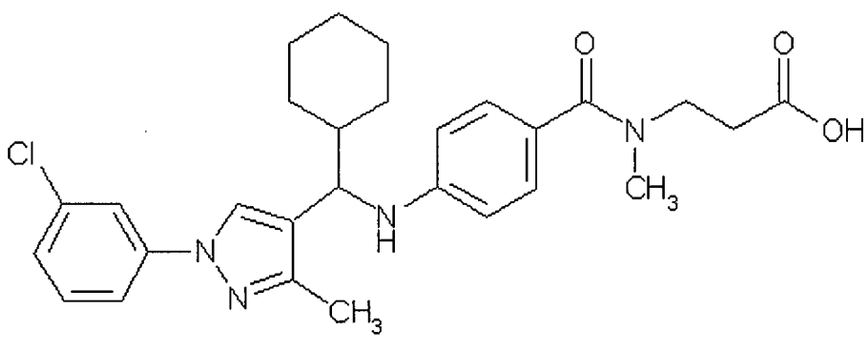
1085

(acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[1-(3-metoxifenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,38 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (3 mL), se añadió solución acuosa 1 N de hidróxido de sodio (1,5 mL) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y el ácido clorhídrico 1 N (1,5 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,17 g, 34%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 2,03 (m, 11 H), 2,35 (s, 3 H), 2,70 (t, J = 6,2 Hz, 2 H), 3,06 (s, 3 H), 3,71 (t, J = 6,2 Hz, 2 H), 3,85 (s, 3 H), 4,19 (d, J = 6,1 Hz, 1 H), 6,50 (d, J = 8,0 Hz, 2 H), 6,76 (dd, J = 7,8, 2,1 Hz, 1 H), 7,09 - 7,37 (m, 5 H), 7,67 (br. s., 1 H).

Ejemplo 71

Ácido 3-[{[4-({[1-(3-clorofenil)-3-metil-1H-pirazol-4-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoico



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(1) 1-(3-clorofenil)-3-metil-1H-pirazol-4-carboxilato de metilo

El 3-metil-1H-pirazol-4-carboxilato de metilo (1,6 g) sintetizado en el Ejemplo 1(3) se disolvió en N,N-dimetilacetamida (30 mL), se añadieron ácido 3-clorofenilborónico (3,58 g), acetato de cobre (5,0 g) y piridina (4,0 mL) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite, se añadió ácido clorhídrico 1 N (50 mL) al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (1,9 g, 67%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,55 (s, 3 H), 3,86 (s, 3 H), 3,87 (s, 3 H), 6,70 - 8,35 (m, 5 H).

(2) 1-(3-clorofenil)-3-metil-1H-pirazol-4-carbaldehído

Una solución (20 mL) de 1-(3-clorofenil)-3-metil-1H-pirazol-4-carboxilato de metilo (1,9 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (80 mL) de hidruro de litio y aluminio (0,29 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla se enfrió con hielo nuevamente y se añadieron sucesivamente agua (0,80 mL), solución acuosa 1 N de

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hidróxido de sodio (4,0 mL) y agua (0,80 mL) gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar un producto crudo (0,65 g) de 1-(3-clorofenil)-3-metil-1H-pirazol-4-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (30 mL), se añadió dióxido de manganeso (2,0 g) y la mezcla se calentó durante 30 min con una trampa de Dean-Stark. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y dióxido de manganeso se recogió por filtración. El solvente se evaporó a presión reducida para dar el compuesto objeto del título (0,35 g, 23%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,59 (s, 3 H), 3,88 (s, 3 H), 7,20 - 7,80 (m, 4 H), 8,34 (s, 1 H), 10,00 (s, 1 H).

(3) ciclohexil[1-(3-clorofenil)-3-metil-1H-pirazol-4-il]metanol

A una solución (5 mL) de 1-(3-clorofenil)-3-metil-1H-pirazol-4-carbaldehído (0,35 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano bajo enfriamiento con hielo se añadió gota a gota bromuro de ciclohexilmagnesio (2,4 mL, solución 1 M de tetrahidrofurano). Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar

el compuesto objeto del título (0,25 g, 51%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 - 1,97 (m, 12 H), 2,33 (s, 3 H), 4,44 (d, J = 7,2 Hz, 1 H), 7,20 -7,78 (m, 5 H).

(4) ácido 3-[{[4-({ciclohexil[1-(3-clorofenil)-3-metil-1H-pirazol-4-

il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (3 mL) de ciclohexil[1-(3-clorofenil)-3-metil-1H-pirazol-4-il]metanol (0,25 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,10 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y se vertió cuidadosamente solución saturada acuosa de carbonato ácido de sodio (5 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (5 mL), se añadieron yoduro de sodio (0,19 g), carbonato de sodio (0,13 g) y 3-{[(4-

aminofenil)carbonil](metil)amino}propanoato de etilo (0,20 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[1-(3-clorofenil)-3-metil-1H-pirazol-4-

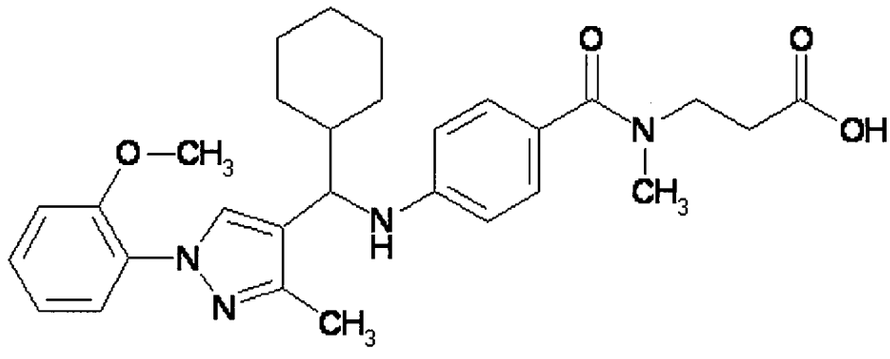
1089

il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,35 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (3 mL), se añadió solución acuosa 1 N de hidróxido de sodio (1,5 mL) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y el ácido clorhídrico 1 N (1,5 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,24 g, 58%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 - 2,07 (m, 11 H), 2,36 (s, 3 H), 2,71 (t, J = 6,4 Hz, 2 H), 3,07 (s, 3 H), 3,72 (t, J = 6,4 Hz, 2 H), 4,19 (d, J = 6,1 Hz, 1 H), 6,48 (d, J = 8,7 Hz, 2 H), 7,12 - 7,73 (m, 7 H).

Ejemplo 72

Ácido 3-[{[4-({[1-(2-metoxifenil)-3-metil-1H-pirazol-4-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoico




(1) 1-(2-metoxifenil)-3-metil-1H-pirazol-4-carboxilato de metilo

1090

El 3-metil-1H-pirazol-4-carboxilato de metilo (7,3 g) sintetizado en el Ejemplo 1(3) se disolvió en N,N-dimetilacetamida (150 mL), se añadieron ácido 2-metoxifenilborónico (15,9 g), acetato de cobre (18,2 g) y piridina (16,2 mL) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite, se añadió ácido clorhídrico 1 N (100 mL) al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (10,3 g, 80%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,55 (s, 3 H), 3,85 (s, 3 H), 6,80 - 8,50 (m, 5 H).

(2) 1-(2-metoxifenil)-3-metil-1H-pirazol-4-carbaldehído

Una solución (50 mL) de 1-(2-metoxifenil)-3-metil-1H-pirazol-4-carboxilato de metilo (10,3 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (350 mL) de hidruro de litio y aluminio (1,6 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla se enfrió con hielo nuevamente y se añadieron sucesivamente agua (4,2 mL), solución acuosa 1 N de hidróxido de sodio (21,0 mL) y agua (4,2 mL) gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar

1091

un producto crudo (2,5 g) de 1-(2-metoxifenil)-3-metil-1H-pirazol-4-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (50 mL), se añadió dióxido de manganeso (1,0 g) y la mezcla se calentó a reflujo con una trampa de Dean-Stark durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y dióxido de manganeso se recogió por filtración. El solvente se evaporó a presión reducida para dar el compuesto objeto del título (2,2 g, 87%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,58 (s, 3 H), 3,92 (s, 3 H), 7,00 - 7,80 (m, 4 H), 8,50 (s, 1 H), 9,99 (s, 1 H).

(3) ciclohexil[1-(2-metoxifenil)-3-metil-1H-pirazol-4-il]metanol

A una solución (15 mL) de 1-(2-metoxifenil)-3-metil-1H-pirazol-4-carbaldehído (1,5 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió gota a gota bajo enfriamiento con hielo bromuro de ciclohexilmagnesio (11,0 mL, solución 1 M de tetrahidrofurano). Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (1,1 g, 53%) en forma de un aceite amarillo pálido.

1092

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 2,10 (m, 12 H), 2,34 (s, 3 H), 3,87 (s, 3 H), 4,43 (dd, J = 7,6, 3,0 Hz, 1 H), 7,00 - 7,75 (m, 4 H), 7,92 (s, 1 H).

(4) ácido 3-[{[4-({ciclohexil[1-(2-metoxifenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (5 mL) de ciclohexil[1-(2-metoxifenil)-3-metil-1H-pirazol-4-il]metanol (0,40 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,15 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y se vertió cuidadosamente solución saturada acuosa de carbonato ácido de sodio (5 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (5,0 mL), se añadieron yoduro de sodio (0,30 g), carbonato de sodio (0,21 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,33 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[1-(2-metoxifenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de

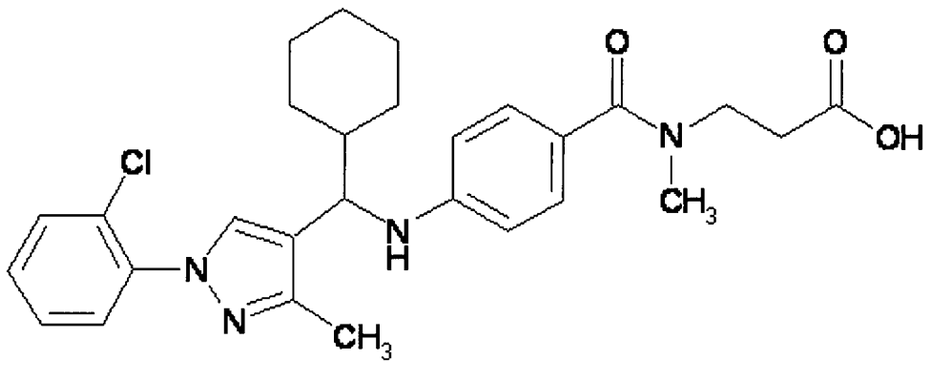
1093

etilo (0,10 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (1,0 mL), se añadió solución acuosa 1 N de hidróxido de sodio (1,0 mL) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y se añadió ácido clorhídrico 1 N (1,0 mL) al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,04 g, 6%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,83 - 1,97 (m, 11 H), 2,26 (s, 3 H), 2,69 (br. s., 2 H), 3,03 (s, 3 H), 3,62 - 3,78 (m, 2 H), 3,82 (s, 3 H), 4,20 (d, J = 6,6 Hz, 1 H), 6,93 - 7,70 (m, 9 H.

Ejemplo 73

Ácido 3-[{[4-({[1-(2-clorofenil)-3-metil-1H-pirazol-4-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoico




(1) 1-(2-clorofenil)-3-metil-1H-pirazol-4-carboxilato de metilo

1094

El 3-metil-1H-pirazol-4-carboxilato de metilo (4,5 g) sintetizado en el Ejemplo 1(3) se disolvió en N,N-dimetilacetamida (100 mL), se añadieron ácido 2-clorofenilborónico (10,0 g), acetato de cobre (11,7 g) y piridina (10,4 mL) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite, se añadió ácido clorhídrico 1 N (100 mL) al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (2,0 g, 25%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,55 (s, 3 H), 3,85 (s, 3 H), 6,79 - 7,40 (m, 5 H).

(2) 1-(2-clorofenil)-3-metil-1H-pirazol-4-carbaldehído

Una solución (20 mL) de 1-(2-clorofenil)-3-metil-1H-pirazol-4-carboxilato de metilo (2,0 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (20 mL) de hidruro de litio y aluminio (0,30 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla se enfrió con hielo nuevamente y se añadieron sucesivamente agua (0,80 mL), solución acuosa 1 N de hidróxido de sodio (4,0 mL) y agua (0,80 mL) gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar

1095

un producto crudo (0,36 g) de 1-(2-clorofenil)-3-metil-1H-pirazol-4-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (10 mL), se añadió dióxido de manganeso (2,0 g) y la mezcla se calentó a reflujo con una trampa de Dean-Stark durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y dióxido de manganeso se recogió por filtración. El solvente se evaporó a presión reducida para dar el compuesto objeto del título (0,27 g, 15%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,59 (s, 3 H), 7,00 - 7,70 (m, 4 H), 8,32 (s, 1 H), 10,02 (s, 1 H).

(3) ciclohexil[1-(2-clorofenil)-3-metil-1H-pirazol-4-il]metanol

A una solución (5 mL) de 1-(2-clorofenil)-3-metil-1H-pirazol-4-carbaldehído (0,27 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió gota a gota bajo enfriamiento con hielo bromuro de ciclohexilmagnesio (2,0 mL, solución 1 M de tetrahidrofurano). Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (0,29 g, 79%) en forma de un aceite amarillo pálido.

1096

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 2,20 (m, 12 H), 2,35 (s, 3 H), 4,45 (d, J = 7,2 Hz, 1 H), 7,20 - 7,60 (m, 4 H), 7,76 (s, 1 H).

(4) ácido 3-[{[4-({ciclohexil[1-(2-clorofenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (5 mL) de ciclohexil[1-(2-clorofenil)-3-metil-1H-pirazol-4-il]metanol (0,29 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,11 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y se vertió cuidadosamente solución saturada acuosa de carbonato ácido de sodio (3 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (5,0 mL), se añadieron yoduro de sodio (0,21 g), carbonato de sodio (0,15 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,24 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[1-(2-clorofenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de

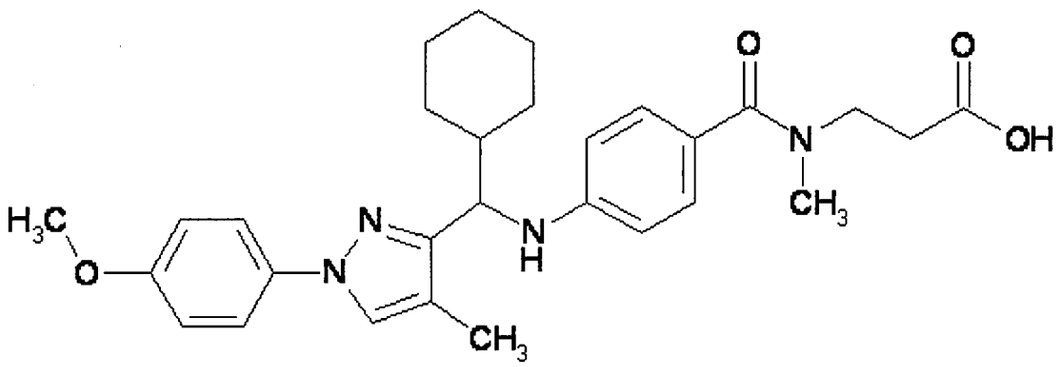
1097

etilo (0,24 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (2,0 mL), se añadió solución acuosa 1 N de hidróxido de sodio (1,0 mL) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,18 g, 37%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 2,08 (m, 11 H), 2,34 (s, 3 H), 2,65 - 2,80 (m, 2 H), 3,08 (s, 3 H), 3,73 (br. s., 2 H), 4,23 (d, J = 6,1 Hz, 1 H), 6,54 (br. s., 2 H), 7,29 - 7,79 (m, 7 H).

Ejemplo 74

Ácido 3-[{[4-({ciclohexil[1-(4-metoxifenil)-4-metil-1H-pirazol-3-il]metil}amino)fenil]carbonil}(metil)amino]propanoico




(1) 1-(4-metoxifenil)-4-metil-1H-pirazol-3-carboxilato de etilo

1098

El 4-metil-1H-pirazol-3-carboxilato de etilo (2,58 g) se disolvió en N,N-dimetilacetamida (50 mL), se añadieron ácido 4-metoxifenilborónico (5,0 g), acetato de cobre (6,0 g) y piridina (5,3 mL) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite, el ácido clorhídrico 1 N (50 mL) se añadió al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (2,7 g, 66%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,21 (t, J = 7,2 Hz, 3 H), 2,33 (s, 3 H), 3,85 (s, 3 H), 4,22 (q, J = 7,2 Hz, 2 H), 6,94 (d, J = 9,0 Hz, 2 H), 7,28 (d, J = 9,0 Hz, 2 H), 7,50 (s, 1 H).

(2) 1-(4-metoxifenil)-4-metil-1H-pirazol-3-carbaldehído

Una solución (10 mL) de 1-(4-metoxifenil)-4-metil-1H-pirazol-3-carboxilato de etilo (2,7 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (20 mL) de hidruro de litio y aluminio (0,40 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla se enfrió con hielo nuevamente y se añadieron sucesivamente agua (1,0 mL), solución acuosa 1 N de hidróxido de sodio (5,0 mL) y agua (1,0 mL) gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar

un producto crudo (1,38 g) de 1-(4-metoxifenil)-4-metil-1H-pirazol-3-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (30 mL), se añadió dióxido de manganeso (2,0 g) y la mezcla se calentó a reflujo con una trampa de Dean-Stark durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y dióxido de manganeso se recogió por filtración. El solvente se evaporó a presión reducida para dar el compuesto objeto del título (0,96 g, 43%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,41 (s, 3 H), 3,87 (s, 3 H), 7,01 (d, J = 8,7 Hz, 2 H), 7,38 (d, J = 8,7 Hz, 2 H), 7,55 (s, 1 H), 9,88 (s, 1 H).

(3) ciclohexil[1-(4-metoxifenil)-4-metil-1H-pirazol-3-il]metanol

A una solución (10 mL) de 1-(4-metoxifenil)-4-metil-1H-pirazol-3-carbaldehído (0,96 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió gota a gota bajo enfriamiento con hielo bromuro de ciclohexilmagnesio (6,0 mL, solución 1 M de tetrahidrofurano). Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (0,70 g, 53%) en forma de un aceite amarillo pálido.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,61 - 1,87 (m, 12 H), 2,19 (s, 3 H), 3,86 (s, 3 H), 4,34 (dd, J = 9,7, 4,4 Hz, 1 H), 6,95 (d, J = 9,0 Hz, 2 H), 7,32 (d, J = 9,0 Hz, 2 H), 7,41 (s, 1 H).

(4) ácido 3-[{[4-({ciclohexil[1-(4-metoxifenil)-4-metil-1H-pirazol-3-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (5 mL) de ciclohexil[1-(4-metoxifenil)-4-metil-1H-pirazol-3-il]metanol (0,40 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,15 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y se vertió cuidadosamente solución saturada acuosa de carbonato ácido de sodio (3 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (10,0 mL), se añadieron yoduro de sodio (0,30 g), carbonato de sodio (0,21 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,34 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[1-(4-metoxifenil)-4-metil-1H-pirazol-3-

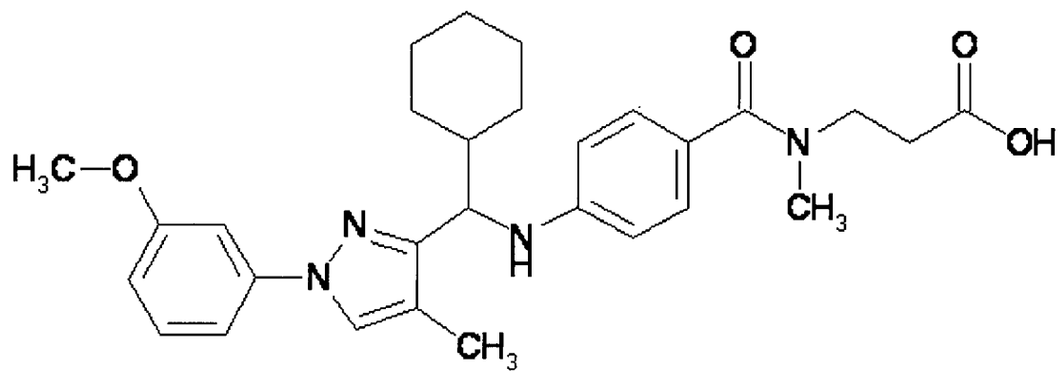
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il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,06 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (1,0 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y el ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,04 g, 6%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 - 2,07 (m, 11 H), 2,18 (s, 3 H), 2,71 (br. s., 2 H), 3,08 (s, 3 H), 3,72 (t, J = 6,4 Hz, 2 H), 3,88 (s, 3 H), 4,24 (d, J = 9,1 Hz, 1 H), 6,30 (d, J = 8,7 Hz, 2 H), 6,94 (d, J = 8,7 Hz, 2 H), 7,10 - 7,26 (m, 4 H), 7,37 (s, 1 H).

Ejemplo 75

Ácido 3-[{[4-({ciclohexil[1-(3-metoxifenil)-4-metil-1H-pirazol-3-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



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(1) 1-(3-metoxifenil)-4-metil-1H-pirazol-3-carboxilato de etilo

El 4-metil-1H-pirazol-3-carboxilato de etilo (2,58 g) se disolvió en N,N-dimetilacetamida (50 mL), se añadieron ácido 3-metoxifenilborónico (5,0 g), acetato de cobre (6,0 g) y piridina (5,3 mL) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite, el ácido clorhídrico 1 N (50 mL) se añadió al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (1,9 g, 46%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,43 (t, J = 7,2 Hz, 3 H), 2,37 (s, 3 H), 3,87 (s, 3 H), 4,43 (q, J = 7,2 Hz, 2 H), 6,94 - 7,50 (m, 5 H).

(2) 1-(3-metoxifenil)-4-metil-1H-pirazol-3-carbaldehído

Una solución (5 mL) de 1-(3-metoxifenil)-4-metil-1H-pirazol-3-carboxilato de etilo (1,9 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (20 mL) de hidruro de litio y aluminio (0,29 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla se enfrió con hielo nuevamente y agua (0,76 mL), solución acuosa 1 N de hidróxido de sodio (3,8 mL) y agua (0,76 mL) se añadieron sucesivamente gota a gota para

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neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar un producto crudo (0,99 g) de 1-(3-metoxifenil)-4-metil-1H-pirazol-3-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (15 mL), se añadió dióxido de manganeso (0,32 g) y la mezcla se calentó a reflujo con una trampa de Dean-Stark durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y dióxido de manganeso se recogió por filtración. El filtrado se concentró a presión reducida para dar el compuesto objeto del título (0,84 g, 54%) en forma de un sólido amarillo.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,39 (s, 3 H), 3,89 (s, 3 H), 6,80 - 7,45 (m, 4 H), 7,74 (s, 1 H), 10,13 (s, 1 H).
(3) ciclohexil[1-(3-metoxifenil)-4-metil-1H-pirazol-3-il]metanol

A una solución (10 mL) de 1-(3-metoxifenil)-4-metil-1H-pirazol-3-carbaldehído (0,84 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió gota a gota bajo enfriamiento con hielo bromuro de ciclohexilmagnesio (7,0 mL, solución 1 M de tetrahidrofurano). Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar

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el compuesto objeto del título (0,62 g, 52%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,99 - 2,00 (m, 12 H), 2,12 (s, 3 H), 3,86 (s, 3 H), 4,52 (t, J = 6,6 Hz, 1 H), 6,75 - 7,32 (m, 4 H), 7,64 (s, 1 H).

(4) ácido 3-[{[4-({ciclohexil[1-(3-metoxifenil)-4-metil-1H-pirazol-3-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (5 mL) de ciclohexil[1-(3-metoxifenil)-4-metil-1H-pirazol-3-il]metanol (0,52 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,19 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y se vertió cuidadosamente solución saturada acuosa de carbonato ácido de sodio (3 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (10,0 mL), se añadieron yoduro de sodio (0,39 g), carbonato de sodio (0,28 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,38 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar

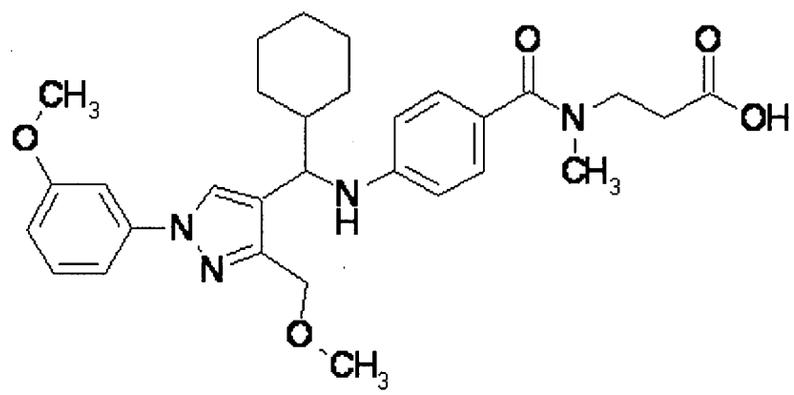
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3-[{[4-({ciclohexil[1-(3-metoxifenil)-4-metil-1H-pirazol-3-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,16 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (2,0 mL), se añadió solución acuosa 1 N de hidróxido de sodio (1,5 mL) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y el ácido clorhídrico 1 N (1,5 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,09 g, 11%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 - 2,06 (m, 11 H), 2,09 (s, 3 H), 2,73 (t, J = 6,2 Hz, 2 H), 3,08 (s, 3 H), 3,72 (t, J = 6,2 Hz, 2 H), 3,87 (s, 3 H), 4,40 (d, J = 7,2 Hz, 1 H), 6,62 (d, J = 8,7 Hz, 2 H), 6,78 (dd, J = 7,8, 2,1 Hz, 1 H), 7,10 - 7,50 (m, 5 H), 7,57 (s, 1 H).

Ejemplo 76

Ácido 3-[{[4-({ciclohexil[1-(3-metoxifenil)-4-metil-1H-pirazol-3-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



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(1) 3-(metoximetil)-1-(3-metoxifenil)-1H-pirazol-4-carboxilato de metilo

A una solución de 3-(metoximetil)-1-fenil-1H-pirazol-4-carboxilato de metilo (2,8 g) sintetizado en el Ejemplo 37(1) en N,N-dimetilacetamida (50 mL) se añadieron ácido 3-metoxifenilborónico (5,0 g), acetato de cobre (6,0 g) y piridina (5,3 mL) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite, el ácido clorhídrico 1 N (50 mL) se añadió al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (1,1 g, 23%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,51 (s, 3 H), 3,87 (s, 3 H), 3,92 (s, 3 H), 4,80 (s, 2 H), 7,29 - 7,93 (m, 4 H), 8,37 (s, 1 H).

(2) 3-(metoximetil)-1-(3-metoxifenil)-1H-pirazol-4-carbaldehído

Una solución (5 mL) de 3-(metoximetil)-1-(3-metoxifenil)-1H-pirazol-4-carboxilato de metilo (1,1 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (10 mL) de hidruro de litio y aluminio (0,25 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla se enfrió con

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hielo nuevamente y agua (0,38 mL), solución acuosa 1 N de hidróxido de sodio (1,9 mL) y agua (0,38 mL) se añadieron sucesivamente gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar un producto crudo (0,68 g) de 3-(metoximetil)-1-(3-metoxifenil)-1H-pirazol-4-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (15 mL), se añadió dióxido de manganeso (1,0 g) y la mezcla se calentó a reflujo con una trampa de Dean-Stark durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y dióxido de manganeso se recogió por filtración. El solvente se evaporó a presión reducida para dar el compuesto objeto del título (0,30 g, 32%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,50 (s, 3 H), 3,88 (s, 3 H), 4,80 (s, 2 H), 6,91 (dd, J = 8,3, 1,5 Hz, 1 H), 7,16 - 7,49 (m, 3 H), 8,40 (s, 1 H), 10,07 (s, 1 H).

(3) ciclohexil[3-(metoximetil)-1-(3-metoxifenil)-1H-pirazol-4-il]metanol

A una solución (5 mL) de 3-(metoximetil)-1-(3-metoxifenil)-1H-pirazol-4-carbaldehído (0,30 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió gota a gota bajo enfriamiento con hielo bromuro de ciclohexilmagnesio (2,0 mL, solución 1 M de tetrahidrofurano). Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se

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extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (0,40 g, cuantitativo) en forma de un aceite amarillo pálido. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,89 - 2,21 (m, 11 H), 3,04 (br.s, 1 H), 3,44 (s, 3 H), 3,87 (s, 3 H), 4,41 (d, J = 7,7 Hz, 1 H), 4,61 (d, J = 3,6 Hz, 2 H), 6,82 (ddd, J = 8,1, 2,5, 0,8 Hz, 1 H), 7,14 - 7,40 (m, 3 H), 7,77 (s, 1 H).

(4) ácido 3-[{[4-({ciclohexil[1-(3-metoxifenil)-4-metil-1H-pirazol-3-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (5 mL) de ciclohexil[3-(metoximetil)-1-(3-metoxifenil)-1H-pirazol-4-il]metanol (0,40 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,14 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y se vertió cuidadosamente solución saturada acuosa de carbonato ácido de sodio (3 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (5,0 mL), se añadieron yoduro de sodio (0,23 g), carbonato de sodio (0,18 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,25 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla

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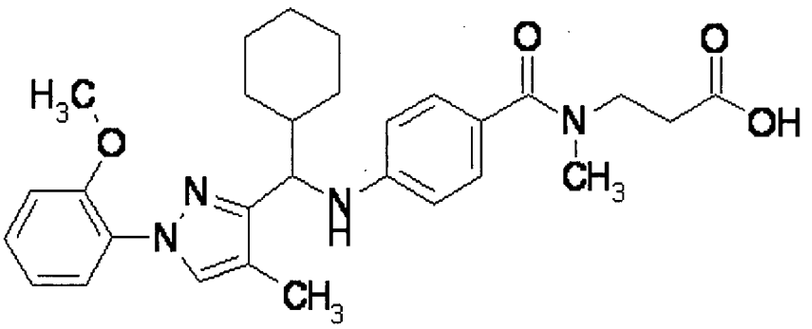
de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[1-(3-metoxifenil)-4-metil-1H-pirazol-3-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,11 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (3,0 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,07 g, 10%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 2,12 (m, 11 H), 2,73 (t, J = 6,5 Hz, 2 H), 3,07 (s, 3 H), 3,41 (s, 3 H), 3,72 (t, J = 6,5 Hz, 2 H), 3,85 (s, 3 H), 4,34 (d, J = 7,2 Hz, 1 H), 4,57 (s, 2 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,79 (dt, J = 8,2, 1,3 Hz, 1 H), 7,11 - 7,38 (m, 5 H), 7,72 (s, 1 H).

Ejemplo 77

Ácido 3-[{[4-({ciclohexil[1-(2-metoxifenil)-4-metil-1H-pirazol-3-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

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(1) 1-(2-metoxifenil)-4-metil-1H-pirazol-3-carboxilato de etilo

El 4-metil-1H-pirazol-3-carboxilato de etilo (4,0 g) se disolvió en N,N-dimetilacetamida (30 mL), se añadieron ácido 2-metoxifenilborónico (7,9 g), acetato de cobre (9,5 g) y piridina (8,4 mL) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite, el ácido clorhídrico 1 N (50 mL) se añadió al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (1,6 g, 25%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,41 (t, J = 7,2 Hz, 3 H), 2,37 (s, 3 H), 3,87 (s, 3 H), 4,43 (q, J = 7,2 Hz, 2 H), 7,00 - 7,45 (m, 4 H), 7,78 (s, 1 H).

(2) 1-(2-metoxifenil)-4-metil-1H-pirazol-3-carbaldehído

Una solución (5 mL) de 1-(2-metoxifenil)-4-metil-1H-pirazol-3-carboxilato de etilo (1,6 g) sintetizada en el

punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (10 mL) de hidruro de litio y aluminio (0,50 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, se enfrió nuevamente con hielo y se añadieron agua (1,3 mL), solución acuosa 1 N de hidróxido de sodio (6,5 mL) y agua (1,3 mL) sucesivamente gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar un producto crudo (0,79 g) de 1-(2-metoxifenil)-4-metil-1H-pirazol-3-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (20 mL), se añadió dióxido de manganeso (2,0 g) y la mezcla se calentó a reflujo con una trampa de Dean-Stark durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y el dióxido de manganeso se recogió por filtración. El solvente se evaporó a presión reducida para dar el compuesto objeto del título (0,97 g, 70%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,39 (s, 3 H), 3,90 (s, 3 H), 7,00 - 7,45 (m, 3 H), 7,64 - 7,84 (m, 2 H), 10,13 (s, 1 H).

(3)ciclohexil[1-(2-metoxifenil)-4-metil-1H-pirazol-3-il]metanol

A una solución (10 mL) de 1-(2-metoxifenil)-4-metil-1H-pirazol-3-carbaldehído (0,97 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió gota a gota bajo enfriamiento con hielo bromuro de ciclohexilmagnesio (5,0 mL, solución 1 M de tetrahidrofurano). Después de completar la adición gota a gota, se retiró el baño de hielo

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y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (0,56 g, 40%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,99 - 2,00 (m, 12 H), 2,12 (s, 3 H), 3,86 (s, 3 H), 4,52 (t, J = 6,6 Hz, 1 H), 6,75 - 7,32 (m, 4 H), 7,64 (s, 1 H).

(4) ácido 3-[{[4-({ciclohexil[1-(3-metoxifenil)-4-metil-1H-pirazol-3-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (5 mL) de ciclohexil[1-(2-metoxifenil)-4-metil-1H-pirazol-3-il]metanol (0,45 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió cloruro de tionilo (0,17 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, se enfrió con hielo y cuidadosamente se añadió solución saturada acuosa de carbonato de sodio (3 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (10,0 mL), se añadieron yoduro de sodio (0,33 g), carbonato de sodio (0,24 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,38 g)

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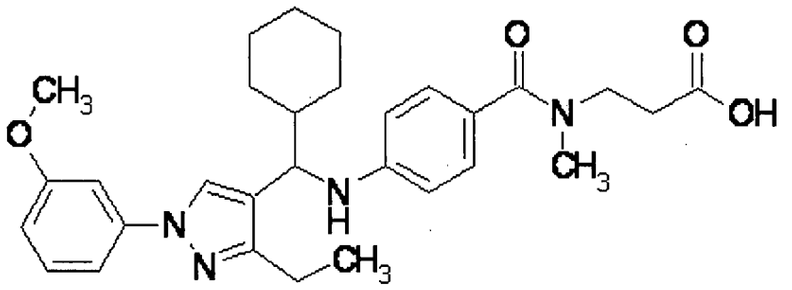
sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[1-(2-metoxifenil)-4-metil-1H-pirazol-3-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,09 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (2,0 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y el ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,06 g, 8%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 - 2,07 (m, 11 H), 2,10 (s, 3 H), 2,73 (t, J = 6,2 Hz, 2 H), 3,09 (s, 3 H), 3,72 (t, J = 6,2 Hz, 2 H), 3,86 (s, 3 H), 4,41 (d, J = 7,2 Hz, 1 H), 6,62 (d, J = 8,3 Hz, 2 H), 6,96 - 7,37 (m, 5 H), 7,63 (d, J = 8,0 Hz, 1 H), 7,70 (s, 1 H).

Ejemplo 78

Ácido 3-[{[4-({ciclohexil[3-etil-1-(3-metoxifenil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

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(1) 3-etil-1-(3-metoxifenil)-1H-pirazol-4-carboxilato de metilo

El 3-etil-1H-pirazol-4-carboxilato de metilo (2,5 g) sintetizado en el Ejemplo 39(1) se disolvió en N,N-dimetilacetamida (50 mL), se añadieron ácido 3-metoxifenilborónico (5,0 g), acetato de cobre (6,0 g) y piridina (5,3 mL) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite, el ácido clorhídrico 1 N (50 mL) se añadió al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (2,3 g, 54%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,32 (t, J = 7,5 Hz, 3 H), 2,98 (q, J = 7,5 Hz, 2 H), 3,86 (s, 3 H), 3,87 (s, 3 H), 6,86 (ddd, J = 8,2, 2,5, 0,9 Hz, 1 H), 7,16 - 7,46 (m, 3 H), 8,32 (s, 1 H).

(2) 3-etil-1-(3-metoxifenil)-1H-pirazol-4-carbaldehído

1115

Una solución (5 mL) de 3-etil-1-(3-metoxifenil)-1H-pirazol-4-carboxilato de metilo (2,3 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (15 mL) de hidruro de litio y aluminio (0,34 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, se enfrió nuevamente con hielo y agua (0,88 mL), solución acuosa 1 N de hidróxido de sodio (4,4 mL), agua (0,88 mL) se añadieron sucesivamente gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar un producto crudo (2,3 g) de 3-etil-1-(3-metoxifenil)-1H-pirazol-4-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (50 mL), el se añadió dióxido de manganeso (4,0 g) y la mezcla se calentó a reflujo con una trampa de Dean-Stark durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, el dióxido de manganeso se recogió por filtración y el solvente se evaporó a presión reducida para dar el compuesto objeto del título (1,9 g, 94%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,35 (t, J = 7,6 Hz, 3 H), 2,99 (q, J = 7,6 Hz, 2 H), 3,88 (s, 3 H), 6,89 (dd, J = 8,3, 1,5 Hz, 1 H), 7,11 - 7,50 (m, 3 H), 8,33 (s, 1 H), 10,00 (s, 1 H).

(3)ciclohexil[3-etil-1-(3-metoxifenil)-1H-pirazol-4-il]metanol

A una solución (20 mL) de 3-etil-1-(3-metoxifenil)-1H-pirazol-4-carbaldehído (1,9 g) sintetizado en el punto (2)

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antes mencionado en tetrahidrofurano se añadió gota a gota bajo enfriamiento con hielo bromuro de ciclohexilmagnesio (12,0 mL, solución 1 M de tetrahidrofurano). Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida para dar un producto crudo (2,6 g, cuantitativo) del compuesto objeto del título en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 - 1,98 (m, 14 H), 2,71 (q, J = 7,5 Hz, 2 H), 3,60 (br,s., 1 H), 3,87 (s, 3 H), 4,44 (d, J = 7,3 Hz, 1 H), 6,78 (ddd, J = 8,1, 2,4, 0,9 Hz, 1 H), 7,14 - 7,38 (m, 3 H), 7,78 (s, 1 H).

(4) ácido 3-[{[4-({ciclohexil[3-etil-1-(3-metoxifenil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (5 mL) de ciclohexil[3-etil-1-(3-metoxifenil)-1H-pirazol-4-il]metanol (0,31 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió cloruro de tionilo (0,13 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, se enfrió con hielo y cuidadosamente se añadió solución saturada acuosa de carbonato ácido de sodio (3 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida

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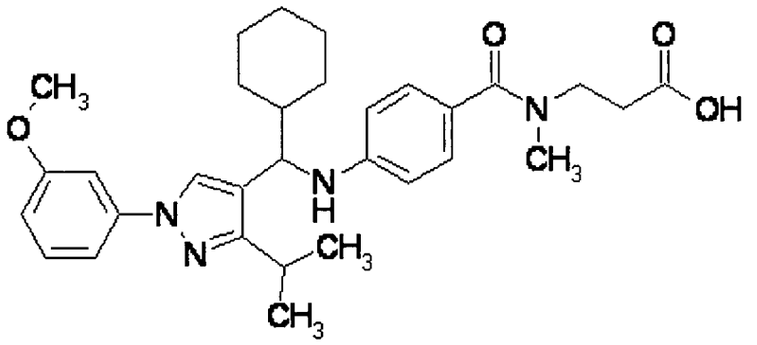
(10,0 mL), se añadieron yoduro de sodio (0,23 g), carbonato de sodio (0,15 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,25 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[3-etil-1-(3-metoxifenil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,16 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (3,0 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,12 g, 23%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 - 2,07 (m, 14 H), 2,62 - 2,81 (m, 4 H), 3,07 (s, 3 H), 3,72 (t, J = 6,0 Hz, 2 H), 3,85 (s, 3 H), 4,22 (d, J = 5,8 Hz, 1 H), 6,51 (d, J = 8,5 Hz, 2 H), 6,76 (dt, J = 8,2, 1,2 Hz, 1 H), 7,10 - 7,37 (m, 5 H), 7,65 (s, 1 H).

Ejemplo 79

Ácido 3-[{[4-({ciclohexil[1-(3-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

1118



(1) 1-(3-metoxifenil)-3-(propan-2-il)-1H-pirazol-4-carboxilato de metilo

El 3-(1-metiletil)-1H-pirazol-4-carboxilato de metilo (2,8 g) sintetizado en el Ejemplo 7(1) se disolvió en N,N-dimetilacetamida (50 mL), se añadieron ácido 3-metoxifenilborónico (5,0 g), acetato de cobre (6,0 g) y piridina (5,3 mL) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite, ácido clorhídrico 1 N (50 mL) se añadió al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (3,4 g, 75%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,36 (d, J = 7,0 Hz, 6 H), 3,56 - 3,59 (m, 1 H), 3,85 (s, 3 H), 3,87 (s, 3 H), 6,85 (ddd, J = 8,1, 2,5, 1,0 Hz, 1 H), 7,18 - 7,45 (m, 3 H), 8,31 (s, 1 H).

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(2) 1-(3-metoxifenil)-3-(propan-2-il)-1H-pirazol-4-carbaldehído

Una solución (15 mL) de 1-(3-metoxifenil)-3-(propan-2-il)-1H-pirazol-4-carboxilato de metilo (3,4 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (35 mL) de hidruro de litio y aluminio (0,48 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, se enfrió nuevamente con hielo y agua (1,25 mL), solución acuosa 1 N de hidróxido de sodio (6,3 mL), agua (1,25 mL) se añadieron sucesivamente gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar un producto crudo (2,7 g) de 1-(3-metoxifenil)-3-(propan-2-il)-1H-pirazol-4-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (50 mL), se añadió dióxido de manganeso (3,0 g) y la mezcla se calentó a reflujo con una trampa de Dean-Stark durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y dióxido de manganeso se recogió por filtración. El solvente se evaporó a presión reducida para dar el compuesto objeto del título (2,6 g, 84%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,39 (d, J = 6,8 Hz, 6 H), 3,48 - 3,52 (m, 1 H), 3,88 (s, 3 H), 6,88 (dd, J = 7,8, 2,1 Hz, 1 H), 7,09 - 7,45 (m, 3 H), 8,33 (s, 1 H), 10,02 (s, 1 H).

(3) ciclohexil[1-(3-metoxifenil)-3-(propan-2-il)-1H-pirazol-4-il]metanol

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A una solución (20 mL) de 1-(3-metoxifenil)-3-(propan-2-il)-1H-pirazol-4-carbaldehído (2,6 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió gota a gota bromuro de ciclohexilmagnesio (15,0 mL, solución 1 M de tetrahidrofurano) bajo enfriamiento con hielo. Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida para dar un producto crudo (2,6 g, 75%) del compuesto objeto del título en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 2,15 (m, 17 H), 3,00 - 3,20 (m, 1 H), 3,86 (s, 3 H), 4,46 (d, J = 7,6 Hz, 1 H), 6,63 - 7,48 (m, 4 H), 7,77 (s, 1 H).

(4) ácido 3-[{[4-({ciclohexil[1-(3-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (5 mL) de ciclohexil[1-(3-metoxifenil)-3-(propan-2-il)-1H-pirazol-4-il]metanol (0,45 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió cloruro de tionilo (0,18 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, se enfrió con hielo y se añadió cuidadosamente una solución saturada acuosa de carbonato ácido de sodio (5 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se

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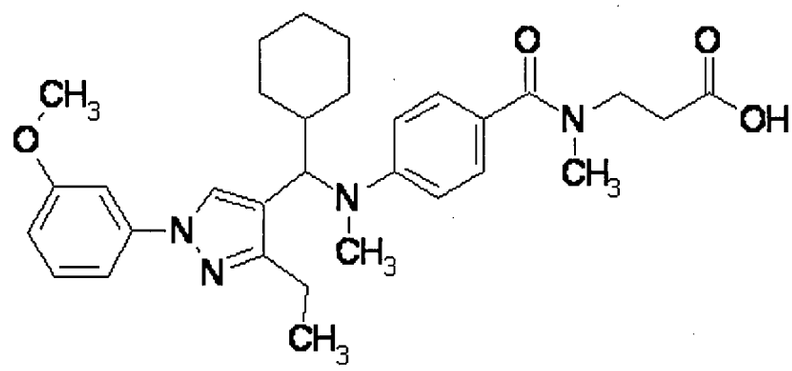
concentró a presión reducida. El residuo se disolvió en dimetilacetamida (10,0 mL), se añadieron yoduro de sodio (0,30 g), carbonato de sodio (0,21 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,34 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[1-(3-metoxifenil)-3-(1-metiletil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,37 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (5,0 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,28 g, 38%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,27 (m, 11 H), 1,30 - 1,40 (m, 6 H), 2,73 (d, J = 6,0 Hz, 2 H), 2,94 - 3,17 (m, 4 H), 3,73 (d, J = 6,0 Hz, 2 H), 3,85 (s, 3 H), 4,26 (d, J = 6,0 Hz, 1 H), 6,52 (d, J = 8,7 Hz, 2 H), 6,75 (ddd, J = 8,2, 2,5, 0,9 Hz, 1 H), 7,10 - 7,32 (m, 5 H), 7,62 (s, 1 H).

Ejemplo 80

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Ácido 3-[({4-[{ciclohexil[3-etil-1-(3-metoxifenil)-1H-pirazol-4-il]metil}(metil)amino]fenil}carbonil)(metil)amino]propanoico



A una solución de 3-[{[4-({ciclohexil[3-etil-1-(3-metoxifenil)-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (1,1 g) sintetizado en el Ejemplo 78(4) en N,N-dimetilacetamida (5 mL) se añadió hidruro de sodio (0,16 g) bajo enfriamiento con hielo y, después de agitar durante 30 min, se añadió yoduro de metilo (0,37 mL). Se retiró el baño de hielo, la mezcla de reacción se agitó a temperatura ambiente durante la noche, se añadió solución acuosa saturada de cloruro de amonio y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera para dar 3-[({4-[{ciclohexil[3-etil-1-(3-metoxifenil)-1H-pirazol-4-il]metil}(metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo (0,23 g, 75%) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (3,0 mL), se añadió solución acuosa 1 N de hidróxido de sodio (1,5 mL) a temperatura

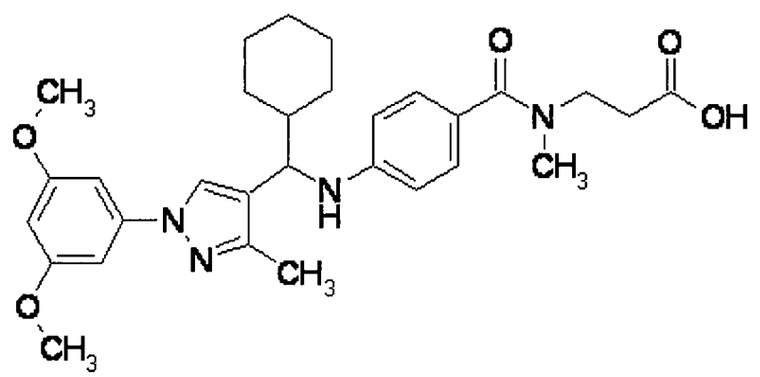
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ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (1,5 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 10:1, relación en volumen) para dar el compuesto objeto del título (0,10 g, 10%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,99 (m, 14 H), 2,17 (s, 3 H), 2,72 (q, J = 7,4 Hz, 2 H), 2,76 - 2,90 (m, 2 H), 3,07 (s, 3 H), 3,75 - 3,85 (m, 5 H), 4,22 (d, J = 5,3 Hz, 1 H), 6,50 (d, J = 8,7 Hz, 2 H), 6,76 (d, J = 8,3 Hz, 1 H), 7,07 - 7,43 (m, 5 H), 7,65 (s, 1 H).

Ejemplo 81

Ácido 3-[{[4-({ciclohexil[1-(3,5-dimetoxifenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



(1) 1-(3,5-dimetoxifenil)-3-metil-1H-pirazol-4-carboxilato de metilo

El 3-metil-1H-pirazol-4-carboxilato de metilo (3,9 g) sintetizado en el Ejemplo 1(3) se disolvió en N,N-dimetilacetamida (50 mL), se añadieron ácido 3,5-dimetoxifenilborónico (10,0 g), acetato de cobre (10,0 g) y piridina (8,9 mL) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite, el ácido clorhídrico 1 N (50 mL) se añadió al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (3,0 g, 40%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,55 (s, 3 H), 3,85 (s, 6 H), 6,41 (t, J = 2,3 Hz, 1 H), 6,83 (d, J = 2,3 Hz, 2 H), 8,30 (s, 1 H).

(2)1-(3,5-dimetoxifenil)-3-metil-1H-pirazol-4-carbaldehído

Una solución (15 mL) de 1-(3,5-dimetoxifenil)-3-metil-1H-pirazol-4-carboxilato de metilo (3,0 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (35 mL) de hidruro de litio y aluminio (0,42 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, se enfrió nuevamente con hielo y agua (1,1 mL), solución acuosa 1 N de hidróxido de sodio (5,5 mL), agua (1,1 mL) se

añadieron sucesivamente gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar un producto crudo (2,7 g) de 1-(3,5-dimetoxifenil)-3-metil-1H-pirazol-4-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (30 mL), se añadió dióxido de manganeso (2,0 g) y la mezcla se calentó a reflujo con una trampa de Dean-Stark durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, el dióxido de manganeso se recogió por filtración y el solvente se evaporó a presión reducida para dar el compuesto objeto del título (2,0 g, 74%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,55 (s, 3 H), 3,85 (s, 6 H), 6,44 (s, 1 H), 6,82 - 6,84 (m, 2 H), 8,30 (s, 1 H), 9,98 (s, 1 H).

(3)ciclohexil[1-(3,5-dimetoxifenil)-3-metil-1H-pirazol-4-il]metanol

A una solución (10 mL) de 1-(3,5-dimetoxifenil)-3-metil-1H-pirazol-4-carbaldehído (2,0 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió gota a gota bromuro de ciclohexilmagnesio (15,0 mL, solución 1 M de tetrahidrofurano) bajo enfriamiento con hielo. Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice

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(acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (2,6 g, 40%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,89 - 2,00 (m, 12 H), 2,33 (s, 3 H), 3,84 (s, 6 H), 4,40 - 4,45 (m, 1 H), 6,34 (t, J = 2,1 Hz, 1 H), 6,81 (d, J = 2,3 Hz, 2 H), 7,76 (s, 1 H).

(4) ácido 3-[{[4-({ciclohexil[1-(3,5-dimetoxifenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (20 mL) de ciclohexil[1-(3,5-dimetoxifenil)-3-metil-1H-pirazol-4-il]metanol (1,0 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió cloruro de tionilo (0,40 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (15 mL) se añadió cuidadosamente. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (15,0 mL), se añadieron yoduro de sodio (0,67 g), carbonato de sodio (0,45 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,75 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel

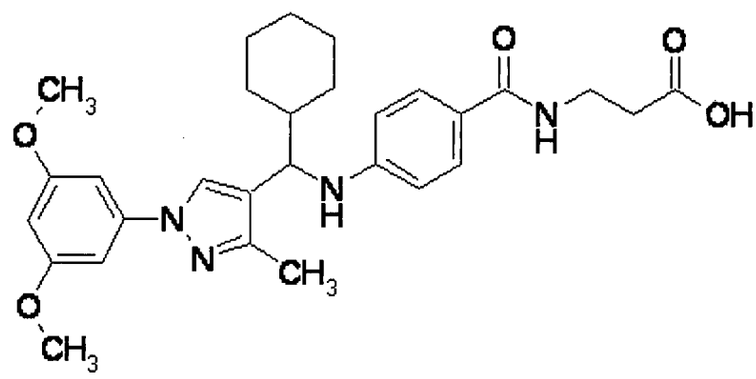
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de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[1-(3,5-dimetoxifenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,74 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (5,0 mL), una solución acuosa 1 N de hidróxido de sodio (3,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (3,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,46 g, 29%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 - 2,02 (m, 11 H), 2,35 (s, 3 H), 2,70 (br. s., 2 H), 3,06 (s, 3 H), 3,71 (t, J = 6,4 Hz, 2 H), 3,82 (s, 6 H), 4,18 (d, J = 5,8 Hz, 1 H), 6,32 (t, J = 2,2 Hz, 1 H), 6,49 (d, J = 8,7 Hz, 2 H), 6,77 (s, 2 H), 7,26 (d, 2 H), 7,64 (s, 1 H).

Ejemplo 82

Ácido 3-({[4-({ciclohexil[1-(3,5-dimetoxifenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico



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A una solución (20 mL) de ciclohexil[1-(3,5-dimetoxifenil)-3-metil-1H-pirazol-4-il]metanol (1,0 g) sintetizado en el Ejemplo 81(3) en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,40 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (15 mL) se añadió cuidadosamente. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (15,0 mL), se añadieron yoduro de sodio (0,67 g), carbonato de sodio (0,45 g) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,70 g) sintetizado en el Ejemplo 1(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-({[4-({ciclohexil[1-(3,5-dimetoxifenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoato de etilo (1,3 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (5,0 mL), una solución acuosa 1 N de hidróxido de sodio (3,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y el ácido clorhídrico 1 N (3,0 mL) se añadió al residuo. El precipitado se lavó con

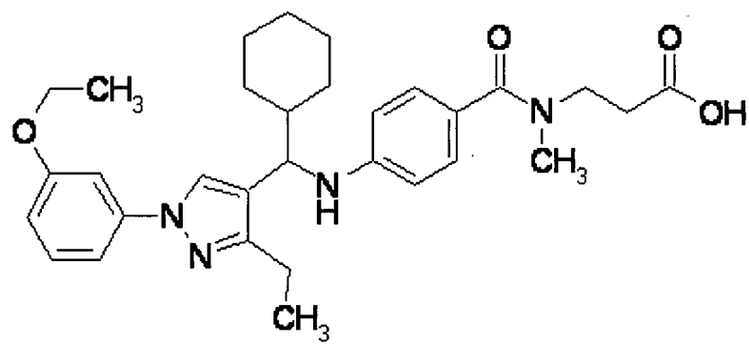
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agua para dar el compuesto objeto del título (0,65 g, 42%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 1,98 (m, 11 H), 2,35 (s, 3 H), 2,65 (t, J = 6,0 Hz, 2 H), 3,66 (d, J = 6,0 Hz, 2 H), 3,80 (s, 6 H), 4,20 (d, J = 6,0 Hz, 1 H), 6,31 (t, J = 2,2 Hz, 1 H), 6,49 (d, J = 8,7 Hz, 2 H), 6,60 (d, J = 6,0 Hz, 1 H), 6,75 (s, 2 H), 7,53 (d, J = 8,9 Hz, 2 H), 7,62 (s, 1 H).

Ejemplo 83

Ácido 3-[{[4-({ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



(1) 1-(3-etoxifenil)-3-etil-1H-pirazol-4-carboxilato de metilo

El 3-etil-1H-pirazol-4-carboxilato de metilo (6,9 g) sintetizado en el Ejemplo 39(1) se disolvió en N,N-dimetilacetamida (150 mL), se añadieron ácido 3-etoxifenilborónico (15,0 g), acetato de cobre (16,4 g) y piridina (14,5 mL) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite, el ácido clorhídrico 1 N (70 mL) se añadió al filtrado y la mezcla se extrajo con éter dietílico. El

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extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (4,4 g, 36%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,32 (t, J = 7,5 Hz, 3 H), 1,44 (t, J = 7,0 Hz, 3 H), 2,98 (q, J = 7,5 Hz, 2 H), 3,85 (s, 3 H), 4,10 (q, J = 7,0 Hz, 2 H), 6,84 (dd, J = 8,2, 1,6 Hz, 1 H), 7,14 - 7,43 (m, 3 H), 8,31 (s, 1 H).

(2) 1-(3-etoxifenil)-3-etil-1H-pirazol-4-carbaldehído

Una solución (15 mL) de 1-(3-etoxifenil)-3-etil-1H-pirazol-4-carboxilato de metilo (4,4 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (35 mL) de hidruro de litio y aluminio (0,61 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, la mezcla se enfrió con hielo nuevamente y agua (1,6 mL), solución acuosa 1 N de hidróxido de sodio (8,0 mL) y agua (1,6 mL) se añadieron sucesivamente gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar un producto crudo (3,5 g) de 1-(3-etoxifenil)-3-etil-1H-pirazol-4-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (100 mL), se añadió dióxido de manganeso (4,0 g) y la mezcla se calentó a reflujo con una trampa de Dean-Stark durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, el dióxido de

manganeso se recogió por filtración y el solvente se evaporó a presión reducida para dar el compuesto objeto del título (3,4 g, 87%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,29 - 1,50 (m, 6 H), 2,99 (q, J = 7,5 Hz, 2 H), 4,11 (q, J = 7,0 Hz, 2 H), 6,88 (ddd, J = 8,2, 2,4, 0,8 Hz, 1 H), 7,15 - 7,45 (m, 3 H), 8,32 (s, 1 H), 10,00 (s, 1 H).

(3) ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metanol

A una solución (20 mL) de 1-(3-etoxifenil)-3-etil-1H-pirazol-4-carbaldehído (1,7 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió gota a gota bajo enfriamiento con hielo bromuro de ciclohexilmagnesio (12,0 mL, solución 1 M de tetrahidrofurano). Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (2,2 g, 96%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,79 - 1,97 (m, 18 H), 2,71 (q, J = 7,5 Hz, 2 H), 4,07 - 4,21 (m, 2 H), 4,44 (dd, J = 7,3, 2,6 Hz, 1 H), 6,77 (dd, J = 7,9, 2,1 Hz, 1 H), 7,13 - 7,37 (m, 3 H), 7,78 (s, 1 H).

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(4) ácido 3-[{[4-({ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

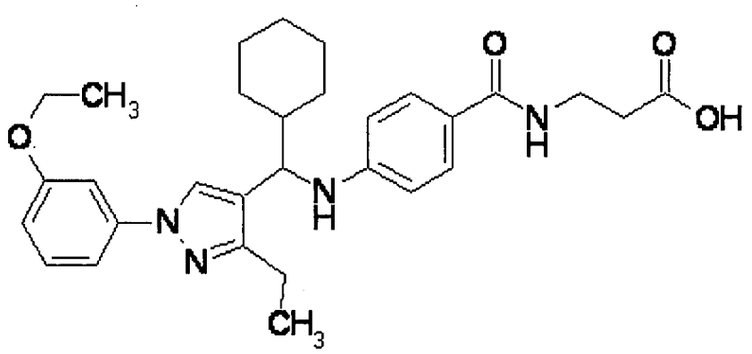
A una solución (10 mL) de ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metanol (0,60 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,24 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (15 mL) se añadió cuidadosamente. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (10,0 mL), se añadieron yoduro de sodio (0,27 g), carbonato de sodio (0,29 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,45 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,7 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (3,0 mL), una solución acuosa 1 N de hidróxido de sodio (3,0 mL) se añadió a temperatura ambiente

y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (3,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,66 g, 69%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 2,30 (m, 17 H), 2,60 - 2,75 (m, 4 H), 3,06 (s, 3 H), 3,72 (t, J = 6,4 Hz, 1 H), 4,08 (q, J = 6,9 Hz, 2 H), 4,22 (d, J = 5,7 Hz, 1 H), 6,50 (d, J = 8,7 Hz, 2 H), 6,74 (dd, J = 8,7, 1,9 Hz, 1 H), 7,09 - 7,34 (m, 5 H), 7,64 (s, 1 H).

Ejemplo 84

Ácido 3-({[4-({ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico



A una solución (10 mL) de ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metanol (0,60 g) sintetizado en el Ejemplo 83(3) en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,24 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y una solución saturada acuosa de carbonato ácido

de sodio (15 mL) se añadió cuidadosamente. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (10,0 mL), se añadieron yoduro de sodio (0,27 g), carbonato de sodio (0,29 g) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,43 g) sintetizado en el Ejemplo 1(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-({[4-({ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoato de etilo (0,6 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (3,0 mL), una solución acuosa 1 N de hidróxido de sodio (3,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (3,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,59 g, 63%) en forma de un sólido incoloro.

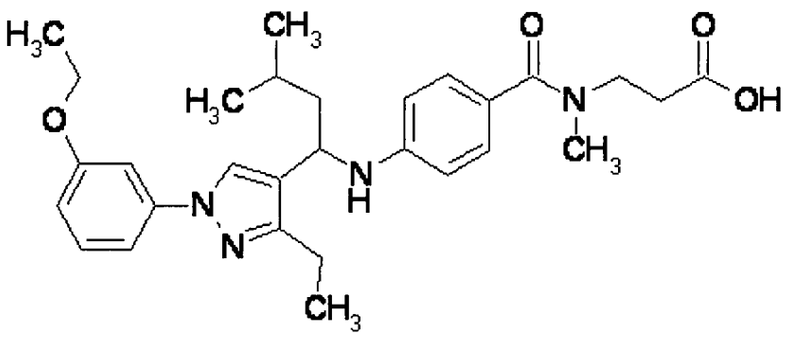
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 - 2,00 (m, 17 H), 2,56 - 2,81 (m, 4 H), 3,64 (q, J = 5,8 Hz, 2 H), 4,06 (q, J = 7,0 Hz, 2 H), 4,24 (d, J = 6,0 Hz, 1 H), 6,50 (d, J = 8,7 Hz, 2 H), 6,54 - 6,62 (m, 1 H), 6,73 (dd, J = 7,7, 2,1 Hz, 1 H),

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7,07 - 7,32 (m, 3 H), 7,53 (d, J = 8,9 Hz, 2 H), 7,63 (s, 1 H).

Ejemplo 85

Ácido 3-[{[4-({1-[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]-3-metilbutil}amino)fenil]carbonil}(metil)amino]propanoico



(1) 1-[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]-3-metilbutan-1-ol

A una solución (20 mL) de 1-(3-etoxifenil)-3-etil-1H-pirazol-4-carbaldehído (1,7 g) sintetizado en el Ejemplo 83(2) en tetrahidrofurano se añadió gota a gota bajo enfriamiento con hielo bromuro de isobutilmagnesio (12,0 mL, solución 1 M de tetrahidrofurano). Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el

compuesto objeto del título (1,4 g, 67%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 (dd, J = 6,4, 2,4 Hz, 6 H), 1,18 - 1,90 (m, 9 H), 2,75 (q, J = 7,6 Hz, 2 H), 4,09 (q, J = 7,0 Hz, 2 H), 4,81 (d, J = 3,6 Hz, 1 H), 6,77 (ddd, J = 8,1, 2,4, 0,9 Hz, 1 H), 7,11 - 7,38 (m, 3 H), 7,79 (s, 1 H).

(2) ácido 3-[{[4-({1-[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]-3-metilbutil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (10 mL) de 1-[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]-3-metilbutan-1-ol (0,71 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,39 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (15 mL) se añadió cuidadosamente. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (15,0 mL), se añadieron yoduro de sodio (0,53 g), carbonato de sodio (0,35 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,59 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar

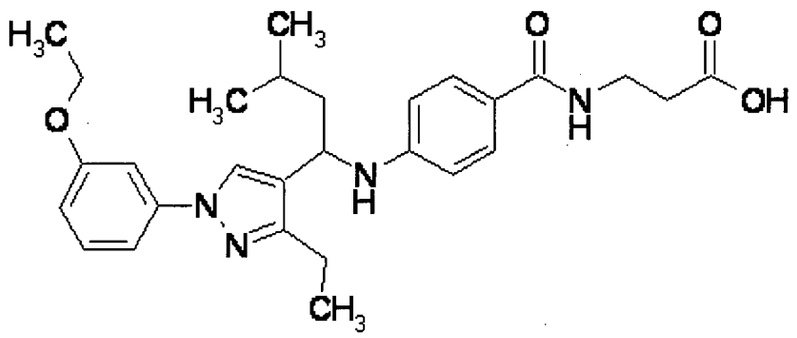
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3-[{[4-({1-[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]-3-metilbutil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,55 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (3,0 mL), una solución acuosa 1 N de hidróxido de sodio (3,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y el ácido clorhídrico 1 N (3,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,46 g, 39%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,89 - 2,00 (m, 15 H), 2,56 - 2,82 (m, 4 H), 3,06 (s, 3 H), 3,72 (t, J = 6,2 Hz, 2 H), 4,08 (q, J = 6,8 Hz, 2 H), 4,46 (t, J = 6,8 Hz, 1 H), 6,55 (d, J = 7,2 Hz, 2 H), 6,75 (dd, J = 8,0, 1,5 Hz, 1 H), 7,05 - 7,38 (m, 5 H), 7,72 (br. s., 1 H).

Ejemplo 86

Ácido 3-({[4-({1-[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]-3-metilbutil}amino)fenil]carbonil}amino)propanoico



A una solución (10 mL) de 1-[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]-3-metilbutan-1-ol (0,71 g) sintetizado en el Ejemplo 85(1) en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,39 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (15 mL) se añadió cuidadosamente. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (15,0 mL), se añadieron yoduro de sodio (0,53 g), carbonato de sodio (0,35 g) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,55 g) sintetizado en el Ejemplo 1(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-({[4-({1-[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]-3-metilbutil}amino)fenil]carbonil}amino)propanoato de etilo (0,56 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (3,0 mL), una solución acuosa 1 N de hidróxido de sodio (3,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (3,0 mL) se añadió al residuo. El precipitado se lavó con

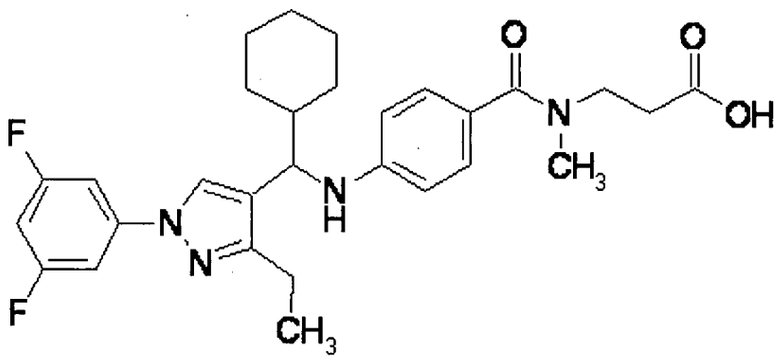
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agua para dar el compuesto objeto del título (0,54 g, 47%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 - 1,10 (m, 6 H), 1,32 (t, J = 7,6 Hz, 3 H), 1,41 (t, J = 7,0 Hz, 3 H), 1,57 - 1,87 (m, 3 H), 2,58 - 2,80 (m, 4 H), 3,67 (q, J = 5,9 Hz, 2 H), 4,07 (q, J = 6,8 Hz, 2 H), 4,48 (t, J = 6,6 Hz, 1 H), 4,75 (br. s., 1 H), 6,53 (d, J = 8,7 Hz, 2 H), 6,66 (t, J = 5,9 Hz, 1 H), 6,74 (dd, J = 8,1, 1,7 Hz, 1 H), 7,07 - 7,33 (m, 3 H), 7,57 (d, J = 8,7 Hz, 2 H), 7,68 (s, 1 H)

Ejemplo 87

Ácido 3-[{[4-({ciclohexil[1-(3,5-difluorofenil)-3-etil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico




(1) 1-(3,5-difluorofenil)-3-metil-1H-pirazol-4-carboxilato de metilo

Una mezcla de 3-oxopentanoato de metilo (5,2 g) y dimetilformamida dimetilacetal (5,6 mL) se agitó a 100 °C durante la noche y la mezcla se dejó enfriar hasta temperatura ambiente. Etanol (100 mL) y clorhidrato de 3,5-

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difluorofenilhidrazina (7,9 g) se añadieron a la mezcla de reacción y la mezcla luego se agitó a 100 °C durante 15 h. Después de enfriar, el etanol se evaporó a presión reducida, agua se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:10, relación en volumen) para dar el compuesto objeto del título (6,5 g, 62%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,21 (t, J = 7,4 Hz, 3 H), 3,03 (q, J = 7,4 Hz, 2 H), 3,87 (s, 3 H), 6,87 - 7,11 (m, 3 H), 8,02 (s, 1 H).

(2) 1-(3,5-difluorofenil)-3-metil-1H-pirazol-4-carbaldehído

Una solución (35 mL) de 1-(3,5-difluorofenil)-3-metil-1H-pirazol-4-carboxilato de metilo (6,5 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (65 mL) de hidruro de litio y aluminio (0,94 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla se enfrió con hielo nuevamente y agua (2,5 mL), solución acuosa 1 N de hidróxido de sodio (12,5 mL) y agua (2,5 mL) se añadieron sucesivamente gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar un producto crudo (3,3 g) de 1-(3,5-difluorofenil)-3-metil-1H-pirazol-4-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (100 mL), el dióxido de manganeso

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(6,0 g) se añadió y la mezcla se calentó a reflujo con una trampa de Dean-Stark durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, el dióxido de manganeso se recogió por filtración y el solvente se evaporó a presión reducida para dar el compuesto objeto del título (3,1 g, 51%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,25 (t, J = 7,6 Hz, 3 H), 3,03 (q, J = 7,6 Hz, 2 H), 6,85 - 7,11 (m, 3 H), 8,07 (s, 1 H), 9,99 (s, 1 H).

(3) ciclohexil[1-(3,5-difluorofenil)-3-metil-1H-pirazol-4-il]metanol

A una solución (10 mL) de 1-(3,5-difluorofenil)-3-metil-1H-pirazol-4-carbaldehído (1,5 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió gota a gota bajo enfriamiento con hielo bromuro de ciclohexilmagnesio (12,0 mL, solución 1 M de tetrahidrofurano). Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (1,9 g, cuantitativo) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,26 (t, J = 7,2 Hz, 3 H), 1,32 - 2,14 (m, 12 H), 2,78 (q, J = 7,2 Hz, 2 H), 4,35 (dd, J = 8,2, 2,9 Hz, 1 H), 6,80 - 7,12 (m, 3 H), 7,62 (s, 1 H).

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(4) ácido 3-[{[4-({ciclohexil[1-(3,5-difluorofenil)-3-etil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (15 mL) de ciclohexil[1-(3,5-difluorofenil)-3-metil-1H-pirazol-4-il]metanol (0,96 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,40 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (10 mL) se añadió cuidadosamente. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (15,0 mL), se añadieron yoduro de sodio (0,68 g), carbonato de sodio (0,48 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,75 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[1-(3,5-difluorofenil)-3-etil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,90 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (3,0 mL), una solución acuosa 1 N de

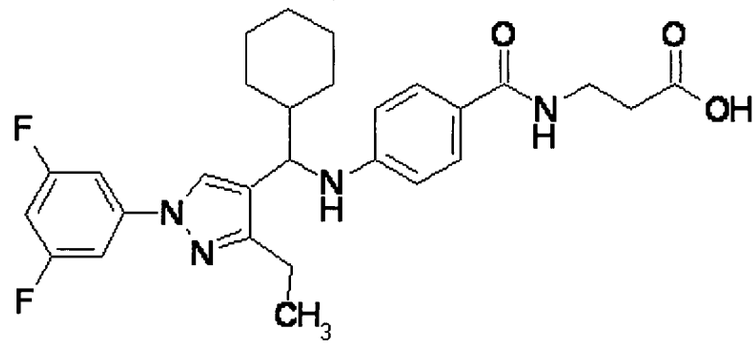
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hidróxido de sodio (3,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y el ácido clorhídrico 1 N (3,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,70 g, 44%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 2,08 (m, 14 H), 2,59 - 2,89 (m, 4 H), 3,08 (s, 3 H), 3,73 (t, J = 6,5 Hz, 2 H), 4,19 (d, J = 6,8 Hz, 1 H), 6,53 (d, J = 8,5 Hz, 2 H), 6,77 - 7,30 (m, 5 H), 7,52 (s, 1 H).

Ejemplo 88

Ácido 3-({[4-({ciclohexil[1-(3,5-difluorofenil)-3-etil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoico




A una solución (15 mL) de ciclohexil[1-(3,5-difluorofenil)-3-metil-1H-pirazol-4-il]metanol (0,96 g) sintetizado en el Ejemplo 87(3) en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,40 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y una solución saturada acuosa de

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carbonato ácido de sodio (10 mL) se añadió cuidadosamente. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (15,0 mL), se añadieron yoduro de sodio (0,68 g), carbonato de sodio (0,48 g) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,70 g) sintetizado en el Ejemplo 1(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-({[4-({ciclohexil[1-(3,5-difluorofenil)-3-etil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)propanoato de etilo (0,80 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (3,0 mL), una solución acuosa 1 N de hidróxido de sodio (3,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (3,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,50 g, 33%) en forma de un sólido incoloro.

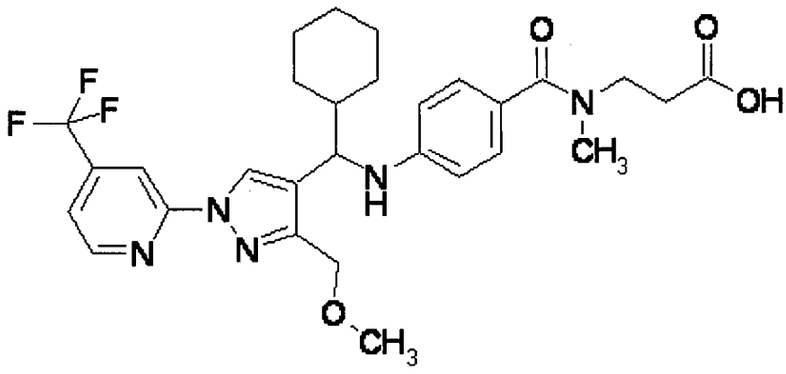
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 (t, J = 7,5 Hz, 3 H), 1,06 - 2,08 (m, 11 H), 2,65 (t, J = 5,7 Hz, 2 H), 2,78 (q, J = 7,5 Hz, 2 H), 3,67 (q, J = 7,0 Hz, 2 H), 4,20 (d, J = 6,8 Hz, 1

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H), 6,52 (d, J = 8,7 Hz, 2 H), 6,57 - 6,68 (m, 1 H), 6,77 - 7,10 (m, 3 H), 7,51 (s, 1 H), 7,55 (d, J = 8,7 Hz, 2 H).

Ejemplo 89

Ácido 3-[({4-[(ciclohexil{3-(metoximetil)-1-[4-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



(1) 3-(metoximetil)-1-[4-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo

A una solución de 3-(metoximetil)-1H-pirazol-4-carboxilato de metilo (1,8 g) sintetizado en el Ejemplo 37(1) en N,N-dimetilformamida (20 mL) se añadieron 2-cloro-4-trifluorometilpiridina (2,0 g) y carbonato de potasio (2,3 g) y la mezcla se agitó a 100 °C durante la noche. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y se filtró a través de celite, se añadió agua al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4,

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relación en volumen) para dar el compuesto objeto del título (0,62 g, 18%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,54 (s, 3 H), 3,89 (s, 3 H), 4,83 (s, 2 H), 7,47 (dd, J = 5,1, 0,9 Hz, 1 H), 8,31 (s, 1 H), 8,61 (d, J = 5,1 Hz, 1 H), 9,04 (s, 1 H).

(2) 3-(metoximetil)-1-[4-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído

Una solución (2 mL) de 3-(metoximetil)-1-[4-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo (0,62 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (5 mL) de hidruro de litio y aluminio (0,10 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla se enfrió con hielo nuevamente y agua (0,2 mL), solución acuosa 1 N de hidróxido de sodio (1,0 mL) y agua (0,2 mL) se añadieron sucesivamente gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar un producto crudo (0,53 g) de 3-(metoximetil)-1-[4-(trifluorometil)piridin-2-il]-1H-pirazol-4-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (30 mL), se añadió dióxido de manganeso (2,0 g) y la mezcla se calentó a reflujo con una trampa de Dean-Stark durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y dióxido de manganeso se recogió por filtración. El solvente se evaporó a presión reducida para dar el compuesto objeto del título (0,59 g, cuantitativo) en forma de un aceite amarillo.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,53 (s, 3 H), 4,83 (s, 2 H), 7,50 (d, J = 4,9 Hz, 1 H), 8,31 (s, 1 H), 8,63 (d, J = 5,1 Hz, 1 H), 9,09 (s, 1 H), 10,10 (s, 1 H).

(3) ciclohexil{3-(metoximetil)-1-[4-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol

A una solución (10 mL) de 3-(metoximetil)-1-[4-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído (0,59 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió gota a gota bajo enfriamiento con hielo bromuro de ciclohexilmagnesio (4,0 mL, solución 1 M de tetrahidrofurano). Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (0,23 g, 30%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,96 (m, 12 H), 3,45 (s, 3 H), 4,43 (d, J = 7,7 Hz, 1 H), 4,58 - 4,65 (m, 2 H), 7,38 (d, J = 0,9 Hz, 1 H), 8,15 - 8,60 (m, 3 H).

(4) ácido 3-[({4-[(ciclohexil{3-(metoximetil)-1-[4-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

A una solución (5 mL) de ciclohexil{3-(metoximetil)-1-[4-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,23 g) sintetizado en el punto (3) antes mencionado en

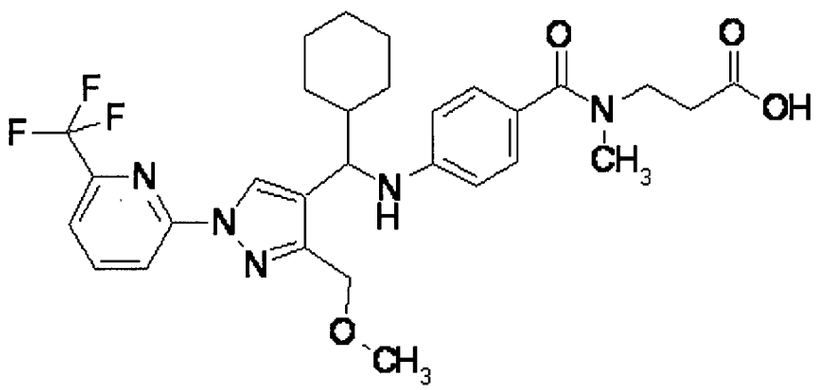
tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,10 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y se añadió cuidadosamente una solución saturada acuosa de carbonato ácido de sodio (5 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (5,0 mL), se añadieron yoduro de sodio (0,14 g), carbonato de sodio (0,10 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,17 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[({4-[(ciclohexil{3-(metoximetil)-1-[4-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo (0,10 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (1,0 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,04 g, 10%) en forma de un sólido amarillo pálido.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 2,18 (m, 11 H), 2,70 (t, J = 6,3 Hz, 2 H), 3,06 (s, 3 H), 3,42 (s, 3 H), 3,71 (t, J = 6,3 Hz, 2 H), 4,36 (d, J = 7,2 Hz, 1 H), 4,57 (d, J = 2,1 Hz, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 7,24 (d, J = 8,7 Hz, 2 H), 7,37 (d, J = 5,3 Hz, 1 H), 8,16 (s, 1 H), 8,36 (s, 1 H), 8,53 (d, J = 5,3 Hz, 1 H).

Ejemplo 90

Ácido 3-[({4-[(ciclohexil{3-(metoximetil)-1-[6-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



(1) 3-(metoximetil)-1-[6-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo

A una solución de 3-(metoximetil)-1H-pirazol-4-carboxilato de metilo (5,1 g) sintetizado en el Ejemplo 37(1) en N,N-dimetilformamida (70 mL) se añadieron 2-cloro-6-trifluorometilpiridina (5,0 g) y carbonato de potasio (6,2 g) y la mezcla se agitó a 100 °C durante la noche. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y se filtró a través de celite, se añadió agua al filtrado y la

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mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (6,5 g, 69%) en forma de cristales incoloros.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,54 (s, 3 H), 3,89 (s, 3 H), 4,83 (s, 2 H), 7,62 (d, J = 7,2 Hz, 1 H), 8,00 - 8,02 (m, 1 H), 8,25 - 8,30 (m, 1 H), 9,06 (s, 1 H).

(2) 3-(metoximetil)-1-[6-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído

Una solución (10 mL) de 3-(metoximetil)-1-[6-(trifluorometil)piridin-2-il]-1H-pirazol-4-carboxilato de metilo (6,5 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (25 mL) de hidruro de litio y aluminio (0,79 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla se enfrió con hielo nuevamente y agua (2,0 mL), solución acuosa 1 N de hidróxido de sodio (10,0 mL) y agua (2,0 mL) se añadieron sucesivamente gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar un producto crudo (6,0 g) de 3-(metoximetil)-1-[6-(trifluorometil)piridin-2-il]-1H-pirazol-4-metanol en forma de un aceite amarillo pálido. Esto se disolvió en tolueno (100 mL), se añadió dióxido de manganeso (3,0 g) y la mezcla se calentó a reflujo con una trampa de Dean-Stark durante 1 h. La mezcla de reacción se

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dejó enfriar hasta temperatura ambiente y dióxido de manganeso se recogió por filtración. El solvente se evaporó a presión reducida para dar el compuesto objeto del título (5,3 g, 90%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,53 (s, 3 H), 4,83 (s, 2 H), 7,66 (d, J = 7,5 Hz, 1 H), 8,05 - 8,08 (m, 1 H), 8,27 (d, J = 8,3 Hz, 1 H), 9,13 (s, 1 H), 10,10 (s, 1 H).

(3) ciclohexil{3-(metoximetil)-1-[6-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol

A una solución (100 mL) de 3-(metoximetil)-1-[6-(trifluorometil)piridin-2-il]-1H-pirazol-4-carbaldehído (5,3 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió gota a gota bajo enfriamiento con hielo bromuro de ciclohexilmagnesio (25,0 mL, solución 1 M de tetrahidrofurano). Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (4,6 g, 67%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 2,22 (m, 11 H), 2,95 (d, J = 6,0 Hz, 1 H), 3,45 (s, 3 H), 4,44 (dd, J = 7,7, 6,0 Hz, 1 H), 4,50 - 4,65 (m, 2 H), 7,53 (d, J = 7,0 Hz, 1 H), 7,93 - 8,00 (m, 1 H), 8,14 (d, J = 8,3 Hz, 1 H), 8,45 (s, 1 H).

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(4) ácido 3-[({4-[(ciclohexil{3-(metoximetil)-1-[6-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

A una solución (5 mL) de ciclohexil{3-(metoximetil)-1-[6-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,50 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,15 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y se añadió cuidadosamente una solución saturada acuosa de carbonato ácido de sodio (5 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (5,0 mL), se añadieron yoduro de sodio (0,37 g), carbonato de sodio (0,26 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,34 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[({4-[(ciclohexil{3-(metoximetil)-1-[6-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo (0,08 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (3,0 mL), una solución acuosa 1 N de

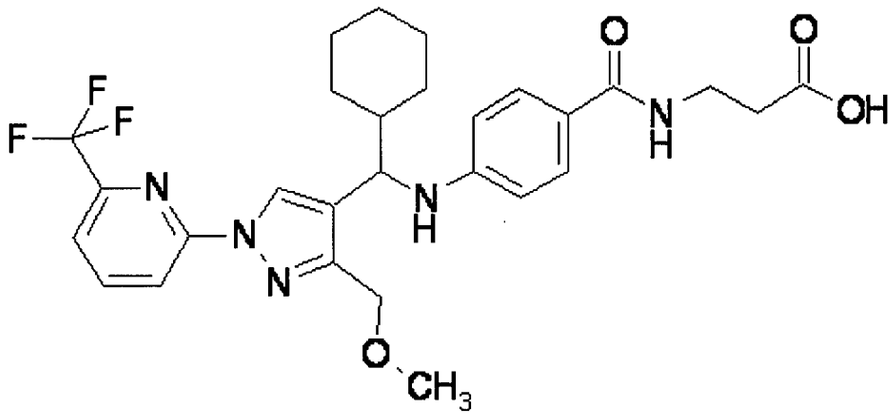
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hidróxido de sodio (1,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,06 g, 7%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 2,19 (m, 11 H), 2,73 (br. s., 2 H), 3,08 (s, 3 H), 3,41 (s, 3 H), 3,72 (t, J = 6,2 Hz, 2 H), 4,36 (d, J = 8,0 Hz, 1 H), 4,57 (d, J = 2,1 Hz, 2 H), 6,58 (d, J = 8,7 Hz, 2 H), 7,20 - 7,30 (m, 2 H), 7,51 - 8,12 (m, 3 H), 8,40 (s, 1 H).

Ejemplo 91

Ácido 3-[({4-[(ciclohexil{3-(metoximetil)-1-[6-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico



A una solución (5 mL) de ciclohexil{3-(metoximetil)-1-[6-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metanol (0,50 g) sintetizado en el Ejemplo 90(3) en tetrahidrofurano

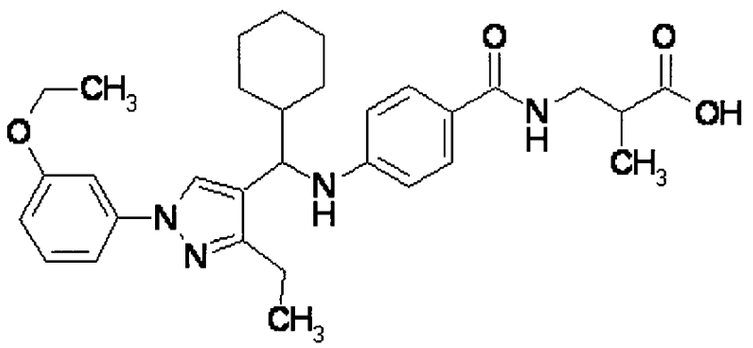
se añadió a temperatura ambiente cloruro de tionilo (0,15 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y se añadió cuidadosamente una solución saturada acuosa de carbonato ácido de sodio (5 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (5,0 mL), se añadieron yoduro de sodio (0,37 g), carbonato de sodio (0,26 g) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,32 g) sintetizado en el Ejemplo 1(2) y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[({4-[(ciclohexil{3-(metoximetil)-1-[6-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoato de etilo (0,07 g) en forma de un aceite amarillo pálido. Esto se disolvió en etanol (3,0 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,06 g, 8%) en forma de un sólido incoloro.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,87 - 2,17 (m, 11 H), 2,67 (t, J = 5,7 Hz, 2 H), 3,41 (s, 3 H), 3,56 - 3,77 (m, 2 H), 4,38 (d, J = 7,6 Hz, 1 H), 4,56 (d, J = 2,3 Hz, 2 H), 6,47 - 6,71 (m, 3 H), 7,46 - 8,11 (m, 5 H), 8,40 (s, 1 H).

Ejemplo 92

Ácido 3-({[4-({ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)-2-metilpropanoico



(1) 4-({ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metil}amino)benzoato de metilo

A una solución (5 mL) de ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metanol (0,64 g) sintetizado en el Ejemplo 83(3) en tetrahidrofurano se añadió a temperatura ambiente cloruro de tionilo (0,22 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (10 mL) se añadió cuidadosamente. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión

reducida. El residuo se disolvió en dimetilacetamida (10,0 mL), se añadieron yoduro de sodio (0,44 g), carbonato de sodio (0,30 g) y 4-aminobenzoato de metilo (0,35 g) y la mezcla se agitó a 70 °C durante la noche. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (0,34 g, 38%) en forma de un aceite amarillo pálido.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,76 - 1,85 (m, 17 H), 2,63 - 2,82 (m, 2 H), 3,82 (s, 3 H), 4,02 - 4,11 (m, 2 H), 4,27 (br. s., 1 H), 6,51 (d, J = 8,9 Hz, 2 H), 6,75 (dd, J = 2,4, 0,9 Hz, 1 H), 7,09 - 7,26 (m, 3 H), 7,64 (s, 1 H), 7,80 (d, J = 8,9 Hz, 2 H).

(2) ácido 4-({ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metil}amino)benzoico

A una solución de 4-({ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metil}amino)benzoato de metilo (0,34 g) sintetizada en el punto (1) antes mencionado en etanol (6,0 mL) se añadió solución acuosa 1 N de hidróxido de sodio (6,0 mL) y la mezcla se agitó a 60 °C durante 6 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (8,0 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un producto crudo (0,33 g, cuantitativo) del compuesto objeto del título en forma de un aceite amarillo.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 2,00 (m, 17 H), 2,72 (q, J = 7,5 Hz, 2 H), 3,99 - 4,11 (m, 2 H), 4,28 (d, J = 5,8 Hz, 1 H), 6,52 (d, J = 8,9 Hz, 2 H), 6,74 (ddd, J = 8,1, 2,5, 0,8 Hz, 1 H), 7,10 - 7,25 (m, 3 H), 7,65 (s, 1 H), 7,84 (d, J = 8,9 Hz, 2 H)

(3) ácido 3-({[4-({ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)-2-metilpropanoico

El ácido 4-({ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metil}amino)benzoico (0,18 g) sintetizado en el punto (2) antes mencionado se disolvió en N,N-dimetilformamida (3 mL), se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (0,11 g), monohidrato de 1-hidroxibenzotriazol (0,09 g) y 3-amino-2-metilpropanoato de metilo (0,07 g) se añadieron a temperatura ambiente y la mezcla se agitó durante la noche. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con éter dietílico. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-({[4-({ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)-2-metilpropanoato de metilo (0,03 g) en forma de un aceite amarillo. Esto se disolvió en etanol (2,0 mL), una solución acuosa 1 N de hidróxido de sodio (0,5 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (0,5 mL) se añadió al residuo. El precipitado se lavó con

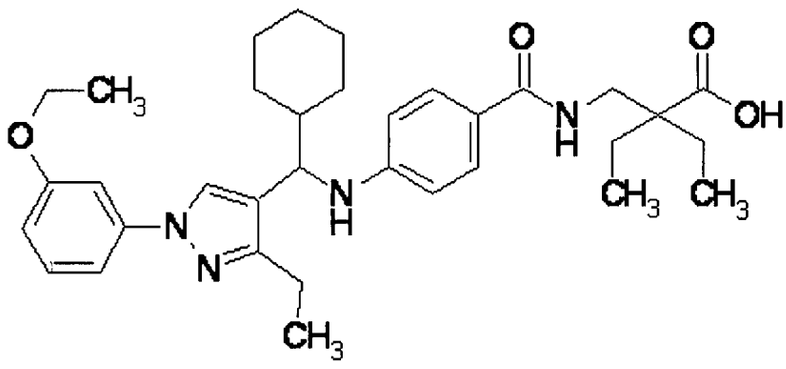
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agua para dar el compuesto objeto del título (0,02 g, 9%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 2,00 (m, 20 H), 2,62 - 2,91 (m, 3 H), 3,59 - 3,75 (m, 2 H), 4,07 (q, J = 6,8 Hz, 2 H), 4,24 (d, J = 6,0 Hz, 1 H), 6,43 - 6,59 (m, 3 H), 6,74 (dd, J = 8,1, 2,4 Hz, 1 H), 7,08 - 7,66 (m, 6 H).

Ejemplo 93

Ácido 2-[({[4-({ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)metil]-2-etilbutanoico



Ácido 4-({Ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metil}amino)benzoico (0,18 g) sintetizado en el Ejemplo 92(2) se disolvió en N,N-dimetilformamida (3 mL), se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (0,11 g), monohidrato de 1-hidroxibenzotriazol (0,09 g), clorhidrato de 2-(aminometil)-2-etilbutanoato de etilo (0,12 g) y trietilamina (0,09 mL) a temperatura ambiente y la mezcla se agitó durante la noche. Se añadió agua a la mezcla de reacción y la mezcla se extrajo

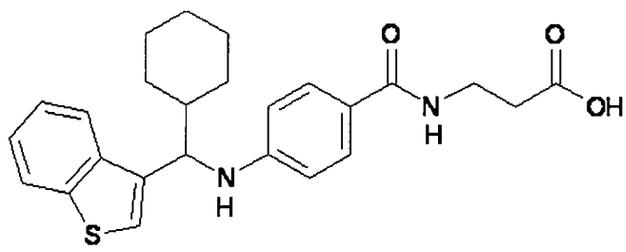
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con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar 2-[({[4-({ciclohexil[1-(3-etoxifenil)-3-etil-1H-pirazol-4-il]metil}amino)fenil]carbonil}amino)metil]-2-etilbutanoato de etilo (0,18 g) en forma de un aceite amarillo. Esto se disolvió en etanol (2,0 mL), una solución acuosa 1 N de hidróxido de sodio (2,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a 60 °C durante la noche. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (2,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,17 g, 74%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (t, J = 7,4 Hz, 6 H), 1,00 - 1,99 (m, 21 H), 2,72 (q, J = 7,5 Hz, 2 H), 3,62 (d, J = 6,2 Hz, 2 H), 4,07 (q, J = 7,0 Hz, 2 H), 4,24 (d, J = 6,0 Hz, 1 H), 6,38 - 6,47 (m, 1 H), 6,51 (d, J = 8,9 Hz, 2 H), 6,73 (ddd, J = 7,1, 1,5, 1,2 Hz, 1 H), 7,09 - 7,24 (m, 3 H), 7,54 (d, J = 8,9 Hz, 2 H), 7,63 (s, 1 H).

Ejemplo A1

Ácido 3-{[(4-{[1-benzotiofen-3-il(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico



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(1) 1-benzotiofen-3-il(ciclohexil)metanol

A una solución (40 mL) de 1-benzotiofen-3-carbaldehído (2,25 g) en tetrahidrofurano se añadió gota a gota solución 1,0 M de bromuro de ciclohexilmagnesio - tetrahidrofurano (20,9 mL) a 0 °C y la mezcla se agitó durante 1,5 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 3:17, relación en volumen) para dar el compuesto objeto del título (2,37 g, 69%) en forma de un aceite anaranjado.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 1,31 (m, 5 H), 1,43 - 1,52 (m, 1 H), 1,60 - 1,73 (m, 2 H), 1,74 - 1,83 (m, 1 H), 1,83 - 1,96 (m, 2 H), 1,97 - 2,05 (m, 1 H), 4,83 (dd, J = 6,8, 3,2 Hz, 1 H), 7,30 - 7,40 (m, 3 H), 7,82 - 7,93 (m, 2 H).

(2) 3-[cloro(ciclohexil)metil]-1-benzotiofeno

A una solución de 1-benzotiofen-3-il(ciclohexil)metanol (2,32 g) sintetizada con anterioridad en tolueno (25 mL) se añadió gota a gota cloruro de tionilo (824 µL) y la mezcla se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se vertió en solución saturada acuosa de carbonato ácido de sodio helada y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó

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sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (2,42 g, 97%) en forma de un aceite anaranjado.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,34 (m, 5 H), 1,46 - 1,56 (m, 1 H), 1,60 - 1,72 (m, 2 H), 1,76 - 1,86 (m, 1 H), 2,10 - 2,28 (m, 2 H), 5,03 (d, J = 8,1 Hz, 1 H), 7,32 - 7,43 (m, 3 H), 7,82 - 7,93 (m, 2 H).

(3) ácido 4-{[1-benzotiofen-3-il(ciclohexil)metil]amino}benzoico

A una mezcla de 3-[cloro(ciclohexil)metil]-1-benzotiofeno (2,42 g) sintetizado con anterioridad, 4-aminobenzoato de metilo (2,77 g), yoduro de sodio (2,74 g) y N,N-dimetilacetamida (50 mL) se añadió carbonato de sodio (1,94 g) y la mezcla se agitó bajo una atmósfera de argón a 100 °C durante la noche. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:3, relación en volumen) para dar un aceite de color amarillo pálido. A una mezcla del aceite obtenido, tetrahidrofurano (20 mL) y etanol (20 mL) se añadió solución acuosa 1 N de hidróxido de sodio (20 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo. La mezcla de reacción se concentró a presión reducida y el residuo se disolvió en agua (40 mL) y ácido clorhídrico 1 N (20 mL) se añadió a 0 °C. El precipitado resultante se

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recogió por filtración para dar el compuesto objeto del título (1,80 g, 54%) en forma de un sólido blanco.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,35 (m, 5 H), 1,60 - 2,03 (m, 6 H), 4,69 (d, J = 5,7 Hz, 1 H), 6,43 - 6,53 (m, 2 H), 7,22 (s, 1 H), 7,32 - 7,47 (m, 2 H), 7,73 - 7,91 (m, 4 H).

(4) ácido 3-{[(4-{[1-benzotiofen-3-il(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico

A una mezcla de ácido 4-{[1-benzotiofen-3-il(ciclohexil)metil]amino}benzoico (250 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (126 mg), monohidrato de 1-hidroxibenzotriazol (126 mg), trietilamina (114 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (157 mg) y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar un aceite de color amarillo pálido. A una mezcla del aceite obtenido, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1 mL) y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró a presión reducida y el residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1 mL) se añadió a 0 °C. El

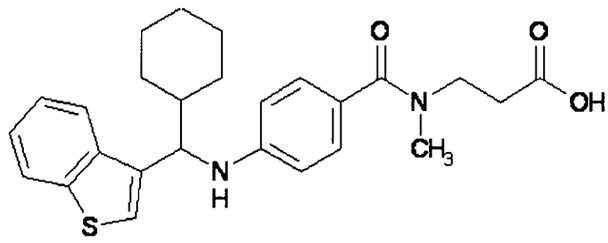
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precipitado resultante se recogió por filtración para dar el compuesto objeto del título (201 mg, 67%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 1,32 (m, 5 H), 1,57 - 1,81 (m, 4 H), 1,81 - 1,99 (m, 2 H), 2,57 (t, J = 5,7 Hz, 2 H), 3,53 - 3,63 (m, 2 H), 4,63 (d, J = 5,7 Hz, 1 H), 6,42 (d, J = 8,7 Hz, 2 H), 6,62 (t, J = 6,1 Hz, 1 H), 7,18 (s, 1 H), 7,31 - 7,46 (m, 4 H), 7,80 - 7,89 (m, 2 H).

Ejemplo A2

Ácido 3-{[(4-{[1-benzotiofen-3-il(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico




Usando ácido 4-{[1-benzotiofen-3-il(ciclohexil)metil]amino}benzoico (250 mg) sintetizado en el Ejemplo A1(3) y 3-(metilamino)propanoato de etilo (108 mg) y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (220 mg, 71%) en forma de un sólido blanco.

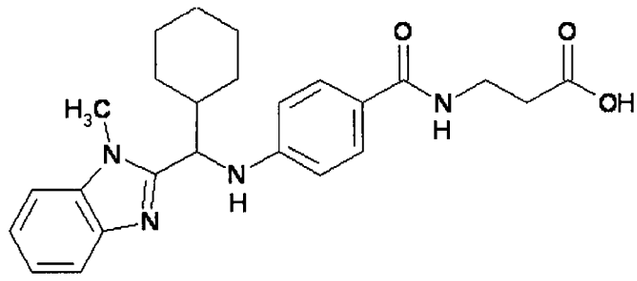
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,34 (m, 5 H), 1,61 - 1,83 (m, 4 H), 1,83 - 2,00 (m, 2 H), 2,67 (t, J = 6,4 Hz, 2 H), 3,02 (s, 3 H), 3,69 (t, J = 6,4 Hz, 2 H), 4,64 (d, J =

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5,7 Hz, 1 H), 6,45 (d, J = 8,7 Hz, 2 H), 7,19 (d, J = 8,7 Hz, 2 H), 7,21 (s, 1 H), 7,33 - 7,45 (m, 2 H), 7,82 - 7,91 (m, 2 H).

Ejemplo A3

Ácido 3-{[(4-{[ciclohexil(1-metil-1H-bencimidazol-2-il)metil]amino}fenil)carbonil]amino}propanoico




(1) ciclohexil(1-metil-1H-bencimidazol-2-il)metanol

Usando 1-metil-1H-benzoimidazol-2-carbaldehído (1,03 g) y de la misma manera que en el Ejemplo A1(1), se obtuvo el compuesto objeto del título (0,58 g, 37%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,05 - 1,30 (m, 5 H), 1,36 - 1,46 (m, 1 H), 1,58 - 2,03 (m, 5 H), 3,77 (s, 3 H), 4,65 (d, J = 7,2 Hz, 1 H), 7,20 - 7,30 (m, 3 H), 7,65 - 7,73 (m, 1 H).

(2) 2-[cloro(ciclohexil)metil]-1-metil-1H-benzoimidazol

Usando ciclohexil(1-metil-1H-bencimidazol-2-il)metanol (0,58 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(2), se obtuvo el compuesto objeto del título (605 mg, 97%) en forma de un sólido marrón.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 - 1,45 (m, 5 H), 1,50 - 1,60 (m, 1 H), 1,62 - 1,75 (m, 2 H), 1,81 - 1,92 (m, 1 H), 2,33 - 2,49 (m, 2 H), 3,87 (s, 3 H), 4,88 (d, J = 9,9 Hz, 1 H), 7,24 - 7,38 (m, 3 H), 7,74 - 7,79 (m, 1 H).

(3) ácido 4-{[ciclohexil(1-metil-1H-bencimidazol-2-il)metil]amino}benzoico

Usando 2-[cloro(ciclohexil)metil]-1-metil-1H-benzoimidazol (605 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(3), se obtuvo el compuesto objeto del título (87,0 mg, 10%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,04 - 1,32 (m, 5 H), 1,39 - 1,51 (m, 1 H), 1,60 - 1,84 (m, 3 H), 2,03 - 2,20 (m, 2 H), 3,90 (s, 3 H), 4,63 - 4,72 (m, 1 H), 5,90 - 6,04 (m, 1 H), 6,69 (d, J = 8,7 Hz, 2 H), 7,25 - 7,39 (m, 3 H), 7,73 - 7,81 (m, 1 H), 7,88 (d, J = 8,7 Hz, 2 H).

(4) ácido 3-{[(4-{[ciclohexil(1-metil-1H-bencimidazol-2-il)metil]amino}fenil)carbonil]amino}propanoico

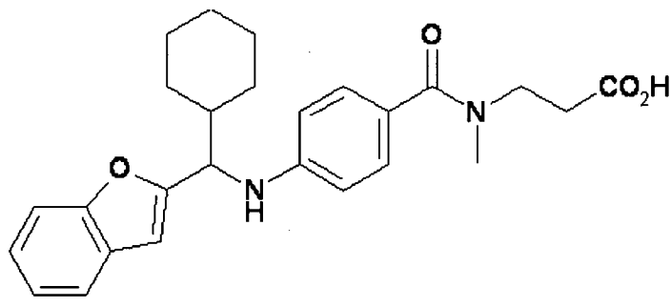
Usando ácido 4-{[ciclohexil(1-metil-1H-bencimidazol-2-il)metil]amino}benzoico (78,3 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (39,5 mg, 42%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 - 1,40 (m, 6 H), 1,59 - 1,71 (m, 2 H), 1,71 - 1,84 (m, 1 H), 1,92 - 2,08 (m, 1 H), 2,13 - 2,26 (m, 1 H), 2,71 (t, J = 5,3 Hz, 2 H), 3,71 - 3,83 (m, 2 H), 3,93 (s, 3 H), 4,59 - 4,71 (m, 1 H), 6,74 (d, J = 8,7 Hz, 2 H), 7,20 - 7,40 (m, 4 H), 7,59 - 7,70 (m, 3 H).

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Ejemplo A4

Ácido 3-{[(4-{[1-benzofuran-2-il(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) 1-benzofuran-2-il(ciclohexil)metanol

Usando 1-benzofuran-2-carbaldehído (2,52 g) y de la misma manera que en el Ejemplo A1(1), se obtuvo el compuesto objeto del título (2,38 g, 60%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 1,36 (m, 5 H), 1,49 - 1,59 (m, 1 H), 1,61 - 2,03 (m, 6 H), 4,50 - 4,57 (m, 1 H), 6,60 (s, 1 H), 7,16 - 7,29 (m, 2 H), 7,43 - 7,47 (m, 1 H), 7,50 - 7,55 (m, 1 H).

(2) 2-[cloro(ciclohexil)metil]-1-benzofurano

Usando 1-benzofuran-2-il(ciclohexil)metanol (1,20 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(2), se obtuvo el compuesto objeto del título (1,17 g, 90%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 - 1,38 (m, 5 H), 1,50 - 1,86 (m, 4 H), 2,08 - 2,23 (m, 2 H), 4,78 (d, J = 8,1 Hz, 1

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H), 6,66 (s, 1 H), 7,12 - 7,32 (m, 2 H), 7,45 - 7,56 (m, 2 H).

(3) ácido 4-{[1-benzofuran-2-il(ciclohexil)metil]amino}benzoico

Usando 2-[cloro(ciclohexil)metil]-1-benzofurano (1,17 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(3), se obtuvo el compuesto objeto del título (523 mg, 32%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,05 - 1,38 (m, 5 H), 1,57 - 1,86 (m, 4 H), 1,88 - 2,03 (m, 2 H), 4,41 - 4,50 (m, 1 H), 4,52 - 4,62 (m, 1 H), 6,53 (s, 1 H), 6,60 (d, J = 8,9 Hz, 2 H), 7,14 - 7,25 (m, 2 H), 7,41 - 7,50 (m, 2 H), 7,85 (d, J = 8,9 Hz, 2 H).

(4) ácido 3-{[(4-{[1-benzofuran-2-il(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico

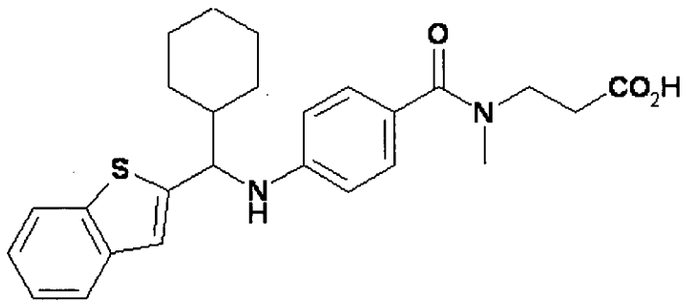
Usando ácido 4-{[1-benzofuran-2-il(ciclohexil)metil]amino}benzoico (250 mg) sintetizado con anterioridad y 3-(metilamino)propanoato de etilo (113 mg) y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (226 mg, 73%) en forma de un sólido de color rojo pálido.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,98 - 1,29 (m, 5 H), 1,39 - 1,50 (m, 1 H), 1,55 - 1,78 (m, 3 H), 1,83 - 2,03 (m, 2 H), 2,43 - 2,54 (m, 2 H), 2,89 (s, 3 H), 3,51 (t, J = 7,3 Hz, 2 H), 4,38 - 4,49 (m, 1 H), 6,46 (d, J = 8,1 Hz, 1 H), 6,67 (d, J = 8,7 Hz, 2 H), 6,75 (s, 1 H), 7,11 (d, J = 8,7 Hz, 2 H), 7,14 - 7,26 (m, 2 H), 7,47 - 7,57 (m, 2 H).

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Ejemplo A5

Ácido 3-{[(4-{[1-benzotiofen-2-il(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) 1-benzotiofen-2-il(ciclohexil)metanol

Usando 1-benzotiofen-2-carbaldehído (2,00 g) y de la misma manera que en el Ejemplo A1(1), se obtuvo el compuesto objeto del título (1,93 g, 64%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 1,35 (m, 5 H), 1,50 - 1,84 (m, 5 H), 1,99 - 2,10 (m, 2 H), 4,70 (dd, J = 7,2, 3,9 Hz, 1 H), 7,15 (s, 1 H), 7,24 - 7,36 (m, 2 H), 7,67 - 7,73 (m, 1 H), 7,77 - 7,83 (m, 1 H).

(2) 2-[cloro(ciclohexil)metil]-1-benzotiofeno

Usando 1-benzotiofen-2-il(ciclohexil)metanol (1,93 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(2), se obtuvo el compuesto objeto del título (1,94 g, 94%) en forma de un sólido marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 - 1,38 (m, 5 H), 1,50 - 2,01 (m, 5 H), 2,15 - 2,25 (m, 1 H), 4,97 (d, J = 7,8 Hz, 1

H), 7,21 (s, 1 H), 7,26 - 7,37 (m, 2 H), 7,66 - 7,73 (m, 1 H), 7,74 - 7,82 (m, 1 H).

(3) ácido 4-{[1-benzotiofen-2-il(ciclohexil)metil]amino}benzoico

Usando 2-[cloro(ciclohexil)metil]-1-benzotiofeno (1,93 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(3), se obtuvo el compuesto objeto del título (719 mg, 27%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,06 - 1,37 (m, 5 H), 1,61 - 1,90 (m, 5 H), 1,91 - 2,04 (m, 1 H), 4,51 - 4,67 (m, 1 H), 6,61 (d, J = 8,8 Hz, 2 H), 7,16 (s, 1 H), 7,21 - 7,36 (m, 2 H), 7,67 (d, J = 7,0 Hz, 1 H), 7,74 (d, J = 7,9 Hz, 1 H), 7,84 (d, J = 8,8 Hz, 2 H).

(4) ácido 3-{[(4-{[1-benzotiofen-2-il(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico

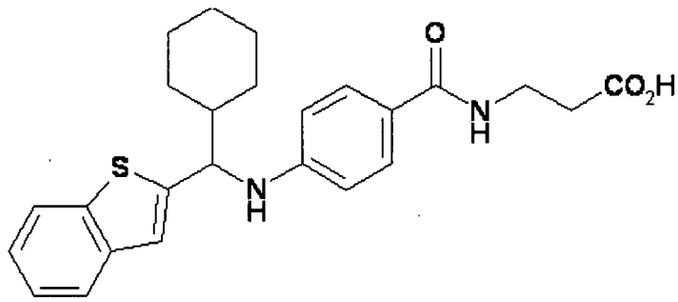
Usando ácido 4-{[1-benzotiofen-2-il(ciclohexil)metil]amino}benzoico (250 mg) sintetizado con anterioridad y 3-(metilamino)propanoato de etilo (108 mg) y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (277 mg, 90%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 1,06 - 1,36 (m, 5 H), 1,62 - 1,87 (m, 5 H), 1,91 - 2,01 (m, 1 H), 2,65 (t, J = 6,4 Hz, 2 H), 3,01 (s, 3 H), 3,69 (t, J = 6,4 Hz, 2 H), 4,49 (d, J = 6,2 Hz, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 7,15 (s, 1 H), 7,18 - 7,35 (m, 4 H), 7,64 - 7,70 (m, 1 H), 7,71 - 7,76 (m, 1 H).

Ejemplo A6

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Ácido 3-{[(4-{[1-benzotiofen-2-il(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico



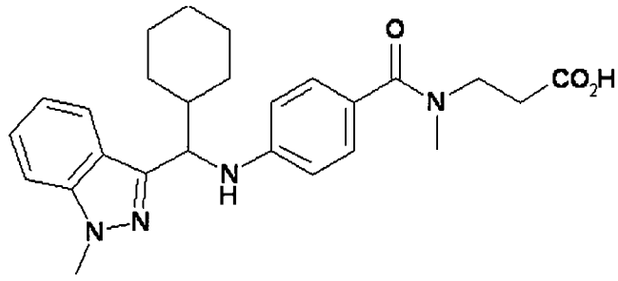

Usando ácido 4-{[1-benzotiofen-2-il(ciclohexil)metil]amino}benzoico (250 mg) sintetizado en el Ejemplo A5(3) y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (275 mg, 92%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,06 - 1,35 (m, 5 H), 1,61 - 1,87 (m, 5 H), 1,89 - 2,01 (m, 1 H), 2,60 (t, J = 5,7 Hz, 2 H), 3,55 - 3,67 (m, 2 H), 4,50 (d, J = 6,2 Hz, 1 H), 6,53 - 6,64 (m, 3 H), 7,14 (s, 1 H), 7,19 - 7,34 (m, 2 H), 7,50 (d, J = 8,7 Hz, 2 H), 7,66 (d, J = 7,3 Hz, 1 H), 7,72 (d, J = 7,9 Hz, 1 H).

Ejemplo A7

Ácido 3-{[(4-{[ciclohexil(1-metil-1H-indazol-3-il)metil]amino}fenil)carbonil](metil)amino}propanoico

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(1) ciclohexil(1-metil-1H-indazol-3-il)metanol

Usando 1-metil-1H-indazol-3-carbaldehído (1,00 g) y de la misma manera que en el Ejemplo A1(1), se obtuvo el compuesto objeto del título (799 mg, 52%) en forma de un aceite de color amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 - 1,37 (m, 5 H), 1,45 - 1,54 (m, 1 H), 1,60 - 1,82 (m, 3 H), 1,84 - 2,03 (m, 2 H), 2,37 - 2,43 (m, 1 H), 4,02 (s, 3 H), 4,83 - 4,89 (m, 1 H), 7,09 - 7,16 (m, 1 H), 7,31 - 7,41 (m, 2 H), 7,80 (d, J = 8,1 Hz, 1 H).

(2) 3-[cloro(ciclohexil)metil]-1-metil-1H-indazol

Usando ciclohexil(1-metil-1H-indazol-3-il)metanol (799 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(2), se obtuvo el compuesto objeto del título (818 mg, 95%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,38 (m, 5 H), 1,40 - 1,50 (m, 1 H), 1,59 - 1,70 (m, 2 H), 1,77 - 1,87 (m, 1 H), 2,18 - 2,40 (m, 2 H), 4,03 (s, 3 H), 5,06 (d, J = 8,7 Hz, 1 H), 7,12 - 7,19 (m, 1 H), 7,32 - 7,42 (m, 2 H), 7,87 (d, J = 8,1 Hz, 1 H).

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(3) ácido 3-{[(4-{[ciclohexil(1-metil-1H-indazol-3-il)metil]amino}fenil)carbonil](metil)amino}propanoico

A una mezcla de 3-[cloro(ciclohexil)metil]-1-metil-1H-indazol (465 mg) sintetizado con anterioridad, 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (531 mg) sintetizado en el Ejemplo 2(2), yoduro de sodio (531 mg) y N,N-dimetilacetamida (10 mL) se añadió carbonato de sodio (375 mg) y la mezcla se agitó bajo una atmósfera de argón a 100 °C durante la noche. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 3:2, relación en volumen) para dar un sólido blanco. A una mezcla del sólido obtenido, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró a presión reducida y el residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (356 mg, 45%) en forma de un sólido blanco.

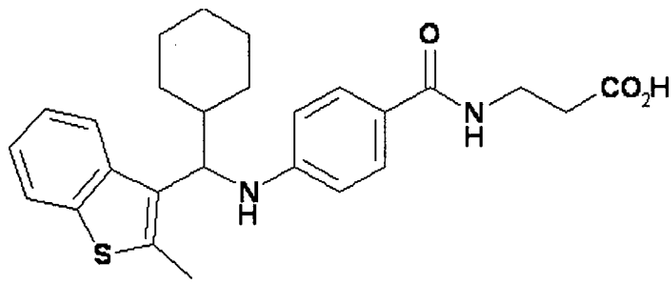
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 - 1,34 (m, 5 H), 1,47 - 1,82 (m, 4 H), 1,89 - 2,10 (m, 2 H), 2,66 (t, J = 6,5 Hz, 2 H), 3,03 (s, 3 H), 3,69 (t, J = 6,5 Hz, 2 H), 4,01 (s, 3 H), 4,70 (d, J = 7,0 Hz, 1 H), 6,60 (d, J = 8,6 Hz, 2 H), 7,06 -

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7,14 (m, 1 H), 7,20 (d, J = 8,6 Hz, 2 H), 7,29 - 7,40 (m, 2 H), 7,74 (d, J = 8,1 Hz, 1 H).

Ejemplo A8

Ácido 3-{[(4-{[ciclohexil(2-metil-1-benzotiofen-3-il)metil]amino}fenil)carbonil]amino}propanoico




(1) 3-bromo-2-metil-1-benzotiofeno

A una solución (50 mL) de 2-metil-1-benzotiofeno (5,00 g) en ácido acético se añadió gota a gota bromo (1,90 mL) a 0 °C y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró a presión reducida, solución saturada acuosa de carbonato ácido de sodio se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (8,02 g, cuantitativo) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,56 (s, 3 H), 7,28 - 7,36 (m, 1 H), 7,36 - 7,44 (m, 1 H), 7,67 - 7,75 (m, 2 H).

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(2) ciclohexil(2-metil-1-benzotiofen-3-il)metanol

El 3-bromo-2-metil-1-benzotiofeno (2,00 g) sintetizado con anterioridad se disolvió en tetrahidrofurano (40 mL), se añadió solución 1,6 M de n-butil-litio - hexano (6,63 mL) se añadió gota a gota a -78 °C. La mezcla se agitó bajo una atmósfera de nitrógeno durante 10 min, se añadió ciclohexancarbaldehído (2,50 mL) y la mezcla se agitó -78 °C durante 30 min y a temperatura ambiente durante 30 min. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 3:17, relación en volumen) para dar el compuesto objeto del título (1,95 g, 85%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,42 (m, 5 H), 1,51 - 1,70 (m, 2 H), 1,71 - 1,92 (m, 3 H), 1,97 - 2,13 (m, 1 H), 2,24 - 2,35 (m, 1 H), 2,54 (s, 3 H), 4,74 (dd, J = 9,1, 2,2 Hz, 1 H), 7,21 - 7,35 (m, 2 H), 7,71 - 7,77 (m, 1 H), 7,97 - 8,05 (m, 1 H).

(3) 3-[cloro(ciclohexil)metil]-2-metil-1-benzotiofeno

Usando ciclohexil(2-metil-1-benzotiofen-3-il)metanol (1,95 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(2), se obtuvo el compuesto objeto del título (1,98 g, 95%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,70 - 0,85 (m, 1 H), 0,96 - 1,40 (m, 4 H), 1,49 - 1,91 (m, 4 H), 2,24 - 2,32 (m, 1 H),

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2,46 - 2,58 (m, 4 H), 4,94 (d, J = 10,5 Hz, 1 H), 7,23 - 7,36 (m, 2 H), 7,70 - 7,75 (m, 1 H), 7,99 (d, J = 7,5 Hz, 1 H).

(4) ácido 4-{[ciclohexil(2-metil-1-benzotiofen-3-il)metil]amino}benzoico

Usando 3-[cloro(ciclohexil)metil]-2-metil-1-benzotiofeno (1,98 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(3), se obtuvo el compuesto objeto del título (1,69 g, 63%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 1,34 (m, 5 H), 1,39 - 1,51 (m, 1 H), 1,62 - 1,71 (m, 2 H), 1,78 - 1,89 (m, 1 H), 1,93 - 2,08 (m, 1 H), 2,09 - 2,20 (m, 1 H), 2,58 (s, 3 H), 4,56 (d, J = 8,5 Hz, 1 H), 6,46 (d, J = 9,0 Hz, 2 H), 7,21 - 7,36 (m, 2 H), 7,69 - 7,84 (m, 4 H).

(5) ácido 3-{[(4-{[ciclohexil(2-metil-1-benzotiofen-3-il)metil]amino}fenil)carbonil]amino}propanoico

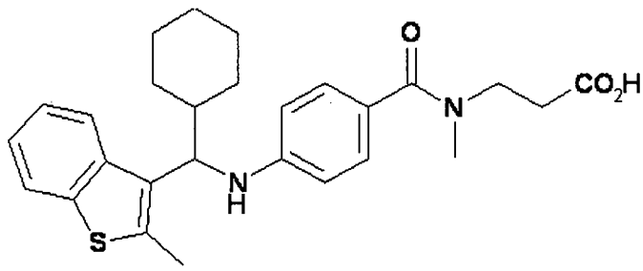
Usando ácido 4-{[ciclohexil(2-metil-1-benzotiofen-3-il)metil]amino}benzoico (300 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (323 mg, 91%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,34 (m, 5 H), 1,40 - 1,51 (m, 1 H), 1,61 - 1,72 (m, 2 H), 1,78 - 1,88 (m, 1 H), 1,92 - 2,07 (m, 1 H), 2,09 - 2,20 (m, 1 H), 2,53 - 2,65 (m, 5 H), 3,54 - 3,65 (m, 2 H), 4,52 (d, J = 8,7 Hz, 1 H), 6,39 - 6,55 (m, 3 H), 7,20 - 7,34 (m, 2 H), 7,39 - 7,48 (m, 2 H), 7,72 (d, J = 8,0 Hz, 1 H), 7,81 (d, J = 7,6 Hz, 1 H).

Ejemplo A9

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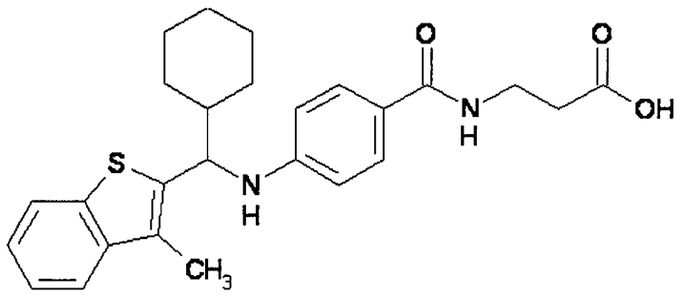
Ácido 3-{[(4-{[ciclohexil(2-metil-1-benzotiofen-3-il)metil]amino}fenil)carbonil](metil)amino}propanoico



Usando ácido 4-{[ciclohexil(2-metil-1-benzotiofen-3-il)metil]amino}benzoico (300 mg) sintetizado en el Ejemplo A8(4) y 3-(metilamino)propanoato de etilo (124 mg) y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (312 mg, 85%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,35 (m, 5 H),1,39 - 1,50 (m, 1 H), 1,61 - 1,73 (m, 2 H), 1,78 - 1,88 (m, 1 H), 1,91 - 2,06 (m, 1 H), 2,09 - 2,20 (m, 1 H), 2,57 (s, 3 H), 2,58 - 2,67 (m, 2 H), 2,99 (s, 3 H), 3,67 (t, J = 6,4 Hz, 1 H), 4,50 (d, J = 8,7 Hz, 1 H), 6,44 (d, J = 8,5 Hz, 2 H), 7,17 (d, J = 8,5 Hz, 1 H), 7,21 - 7,35 (m, 2 H), 7,73 (d, J = 7,2 Hz, 1 H), 7,83 (d, J = 7,6 Hz, 1 H).

Ejemplo A10

Ácido 3-{[(4-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}fenil)carbonil]amino}propanoico



1177

(1) ciclohexil(3-metil-1-benzotiofen-2-il)metanol

Usando 3-metil-1-benzotiofen-2-carbaldehído (2,00 g) y de la misma manera que en el Ejemplo A1(1), se obtuvo el compuesto objeto del título (1,65 g, 56%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 - 1,36 (m, 5 H), 1,41 - 1,52 (m, 1 H), 1,60 - 1,86 (m, 4 H), 2,01 (d, J = 3,3 Hz, 1 H), 2,14 - 2,24 (m, 1 H), 2,37 (s, 3 H), 4,83 (dd, J = 8,1, 3,3 Hz, 1 H), 7,27 - 7,39 (m, 2 H), 7,62 - 7,67 (m, 1 H), 7,77 - 7,82 (m, 1 H).

(2) 2-[cloro(ciclohexil)metil]-3-metil-1-benzotiofeno

Usando ciclohexil(3-metil-1-benzotiofen-2-il)metanol (1,65 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(2), se obtuvo el compuesto objeto del título (1,68 g, 95%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 - 0,99 (m, 1 H), 1,04 - 1,39 (m, 4 H), 1,56 - 1,71 (m, 3 H), 1,77 - 1,88 (m, 1 H), 1,88 - 2,03 (m, 1 H), 2,32 - 2,45 (m, 4 H), 5,09 (d, J = 9,6 Hz, 1 H), 7,29 - 7,39 (m, 2 H), 7,62 - 7,67 (m, 1 H), 7,75 - 7,80 (m, 1 H).

(3) ácido 4-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}benzoico

Usando 2-[cloro(ciclohexil)metil]-3-metil-1-benzotiofeno (1,68 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(3), se obtuvo el compuesto objeto del título (1,63 g, 71%) en forma de un sólido amarillo.

1178

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 1,34 (m, 5 H), 1,53 - 1,87 (m, 5 H), 2,03 - 2,16 (m, 1 H), 2,44 (s, 3 H), 4,54 - 4,63 (m, 1 H), 6,46 (d, J = 8,6 Hz, 2 H), 7,21 - 7,29 (m, 1 H), 7,30 - 7,38 (m, 1 H), 7,63 (d, J = 7,9 Hz, 1 H), 7,69 (d, J = 7,7 Hz, 1 H), 7,75 (d, J = 8,6 Hz, 2 H).

(4) ácido 3-{[(4-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}fenil)carbonil]amino}propanoico

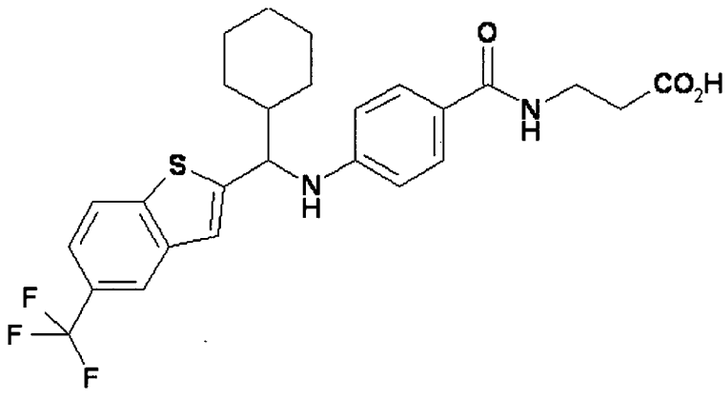
Usando ácido 4-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}benzoico (300 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (275 mg, 77%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,01 - 1,34 (m, 5 H), 1,53 - 1,85 (m, 5 H), 2,03 - 2,14 (m, 1 H), 2,44 (s, 3 H), 2,53 (t, J = 5,6 Hz, 2 H), 3,50 - 3,61 (m, 2 H), 4,54 (d, J = 7,7 Hz, 1 H), 6,48 (d, J = 8,8 Hz, 2 H), 6,58 (t, J = 5,9 Hz, 1 H), 7,20 - 7,27 (m, 1 H), 7,29 - 7,37 (m, 1 H), 7,46 (d, J = 8,8 Hz, 2 H), 7,62 (d, J = 7,5 Hz, 1 H), 7,67 (d, J = 7,5 Hz, 1 H).

Ejemplo A11

Ácido 3-({[4-({ciclohexil[5-(trifluorometil)-1-benzotiofen-2-il]metil}amino)fenil]carbonil}amino)propanoico

1179



(1) 3-metil-5-(trifluorometil)-1-benzotiofen-2-carbaldehído

A una solución (40 mL) de 3-metil-5-(trifluorometil)-1-benzotiofen-2-carboxilato de metilo (2,00 g) en tetrahidrofurano se añadió hidruro de litio y aluminio (292 mg) a 0 °C y la mezcla se agitó durante 1 h. Se añadió agua (300 µL) para neutralizar la reacción, una solución acuosa 1 N de hidróxido de sodio (300 µL) se añadió y la mezcla se agitó a temperatura ambiente durante 3 h. El material insoluble resultante se filtró y el filtrado se concentró a presión reducida para dar un sólido blanco. A una solución del sólido obtenido en tetrahidrofurano (40 mL) se añadió dióxido de manganeso activo (9,00 g) y la mezcla se agitó durante la noche a temperatura ambiente. El dióxido de manganeso se filtró y el filtrado se concentró a presión reducida para dar el compuesto objeto del título (1,15 g, 65%) en forma de un sólido marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 7,69 - 7,75 (m, 1 H), 8,00 - 8,06 (m, 1 H), 8,11 (s, 1 H), 8,21 - 8,25 (m, 1 H), 10,14 (s, 1 H).

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(2) ciclohexil[3-metil-5-(trifluorometil)-1-benzotiofen-2-il]metanol

Usando 3-metil-5-(trifluorometil)-1-benzotiofen-2-carbaldehído (1,15 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(1), se obtuvo el compuesto objeto del título (860 mg, 55%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 - 1,35 (m, 5 H), 1,50 - 1,59 (m, 1 H), 1,62 - 1,85 (m, 4 H), 1,95 - 2,06 (m, 1 H), 2,12 - 2,18 (m, 1 H), 4,75 (d, J = 7,2 Hz, 1 H), 7,22 (s, 1 H), 7,48 - 7,53 (m, 1 H), 7,87 - 7,92 (m, 1 H), 7,97 (s, 1 H).

(3) 2-[cloro(ciclohexil)metil]-3-metil-5-(trifluorometil)-1-benzotiofeno

A una solución de ciclohexil[3-metil-5-(trifluorometil)-1-benzotiofen-2-il]metanol (860 mg) sintetizado con anterioridad en tolueno (20 mL) se añadió cloruro de tionilo (239 µL) y la mezcla se agitó a 100 °C durante 1 h. La mezcla de reacción se vertió en solución saturada acuosa de carbonato ácido de sodio helada y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (806 mg, 89%) en forma de un aceite de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,99 - 1,37 (m, 5 H), 1,58 - 2,01 (m, 5 H), 2,13 - 2,23 (m, 1 H), 4,97 (d, J = 7,8 Hz, 1 H), 7,29 (s, 1 H), 7,51 - 7,56 (m, 1 H), 7,86 - 7,91 (m, 1 H), 7,96 - 7,99 (m, 1 H).

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(4) ácido 4-({ciclohexil[3-metil-5-(trifluorometil)-1-benzotiofen-2-il]metil}amino)benzoico

Usando 2-[cloro(ciclohexil)metil]-3-metil-5-(trifluorometil)-1-benzotiofeno (806 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(3), se obtuvo el compuesto objeto del título (68,7 mg, 7%) en forma de un aceite de color amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,07 - 1,37 (m, 5 H), 1,62 - 1,89 (m, 5 H), 1,90 - 2,00 (m, 1 H), 4,58 (d, J = 6,3 Hz, 1 H), 6,59 (d, J = 8,7 Hz, 2 H), 7,25 (s, 1 H), 7,45 - 7,50 (m, 1 H), 7,82 (d, J = 8,4 Hz, 1 H), 7,84 (d, J = 8,7 Hz, 2 H), 7,93 - 7,96 (m, 1 H).

(5) ácido 3-({[4-({ciclohexil[5-(trifluorometil)-1-benzotiofen-2-il]metil}amino)fenil]carbonil}amino)propanoico

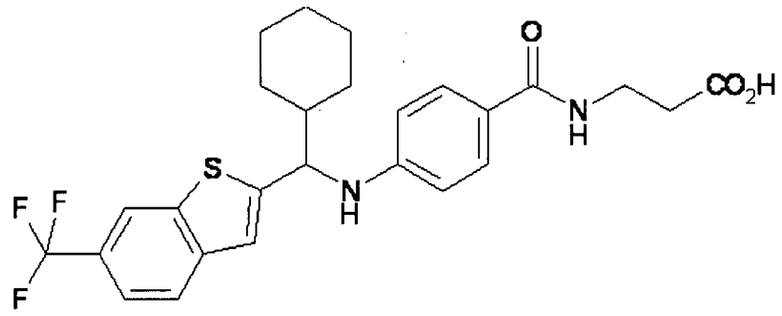
Usando ácido 4-({ciclohexil[3-metil-5-(trifluorometil)-1-benzotiofen-2-il]metil}amino)benzoico (68,7 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (57,8 mg, 73%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,36 (m, 5 H), 1,59 - 1,87 (m, 5 H), 1,88 - 1,99 (m, 1 H), 2,58 (t, J = 5,3 Hz, 2 H), 3,54 - 3,66 (m, 2 H), 4,51 (d, J = 6,4 Hz, 1 H), 6,56 (d, J = 8,3 Hz, 2 H), 6,63 (t, J = 5,7 Hz, 1 H), 7,22 (s, 1 H), 7,43 - 7,49 (m, 1 H), 7,51 (d, J = 8,3 Hz, 2 H), 7,80 (d, J = 8,7 Hz, 1 H), 7,93 (s, 1 H).

Ejemplo A12

Ácido 3-({[4-({ciclohexil[6-(trifluorometil)-1-benzotiofen-2-il]metil}amino)fenil]carbonil}amino)propanoico

1182



(1) 3-metil-6-(trifluorometil)-1-benzotiofen-2-carbaldehído

Usando 3-metil-6-(trifluorometil)-1-benzotiofen-2-carboxilato de metilo (2,07 g) y de la misma manera que en el Ejemplo A11(1), se obtuvo el compuesto objeto del título (1,38 g, 75%) en forma de un sólido marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 7,63 - 7,69 (m, 1 H), 8,06 (d, J = 8,4 Hz, 1 H), 8,08 (s, 1 H), 8,18 - 8,22 (m, 1 H), 10,15 (s, 1 H).

(2) ciclohexil[3-metil-6-(trifluorometil)-1-benzotiofen-2-il]metanol

Usando 3-metil-6-(trifluorometil)-1-benzotiofen-2-carbaldehído (1,38 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(1), se obtuvo el compuesto objeto del título (668 mg, 35%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,99 - 1,35 (m, 5 H), 1,50 - 1,60 (m, 1 H), 1,62 - 1,84 (m, 4 H), 1,94 - 2,04 (m, 1 H), 2,15 - 2,20 (m, 1 H), 4,76 (dd, J = 6,9, 3,6 Hz, 1 H), 7,21 (s, 1 H), 7,52 - 7,58 (m, 1 H), 7,79 (d, J = 8,1 Hz, 1 H), 8,06 - 8,10 (m, 1 H).

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(3) 2-[cloro(ciclohexil)metil]-3-metil-6-(trifluorometil)-1-benzotiofeno

Usando ciclohexil[3-metil-6-(trifluorometil)-1-benzotiofen-2-il]metanol (668 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A11(3), se obtuvo el compuesto objeto del título (659 mg, 93%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 1,37 (m, 5 H), 1,58 - 1,86 (m, 4 H), 1,88 - 2,01 (m, 1 H), 2,12 - 2,22 (m, 1 H), 4,97 (d, J = 7,8 Hz, 1 H), 7,28 (s, 1 H), 7,53 - 7,58 (m, 1 H), 7,80 (d, J = 8,4 Hz, 1 H), 8,05 - 8,08 (m, 1 H).

(4) ácido 4-({ciclohexil[3-metil-6-(trifluorometil)-1-benzotiofen-2-il]metil}amino)benzoico

Usando 2-[cloro(ciclohexil)metil]-3-metil-6-(trifluorometil)-1-benzotiofeno (659 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(3), se obtuvo el compuesto objeto del título (82,5 mg, 10%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,37 (m, 5 H), 1,62 - 1,88 (m, 5 H), 1,90 - 1,99 (m, 1 H), 4,58 (d, J = 6,3 Hz, 1 H), 6,59 (d, J = 8,7 Hz, 2 H), 7,23 (s, 1 H), 7,50 - 7,55 (m, 1 H), 7,76 (d, J = 8,4 Hz, 1 H), 7,84 (d, J = 8,7 Hz, 2 H), 7,99 - 8,02 (m, 1 H).

(5) ácido 3-({[4-({ciclohexil[6-(trifluorometil)-1-benzotiofen-2-il]metil}amino)fenil]carbonil}amino)propanoico

Usando ácido 4-({ciclohexil[3-metil-6-(trifluorometil)-1-benzotiofen-2-il]metil}amino)benzoico (82,5 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo

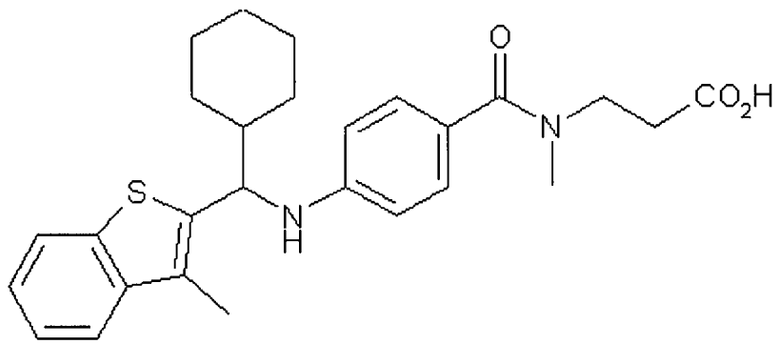
1184

A1(4), se obtuvo el compuesto objeto del título (54,0 mg, 56%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 - 1,35 (m, 5 H), 1,58 - 1,87 (m, 5 H), 1,88 - 1,99 (m, 1 H), 2,53 - 2,63 (m, 2 H), 3,54 - 3,66 (m, 2 H), 4,52 (d, J = 6,1 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,58 - 6,66 (m, 1 H), 7,20 (s, 1 H), 7,46 - 7,55 (m, 3 H), 7,73 (d, J = 8,3 Hz, 1 H), 7,98 (s, 1 H).

Ejemplo A13

Ácido 3-{[(4-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




Usando ácido 4-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}benzoico (300 mg) sintetizado en el Ejemplo A10(3) y 3-(metilamino)propanoato de etilo (124 mg) y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (269 mg, 73%) en forma de un sólido blanco.

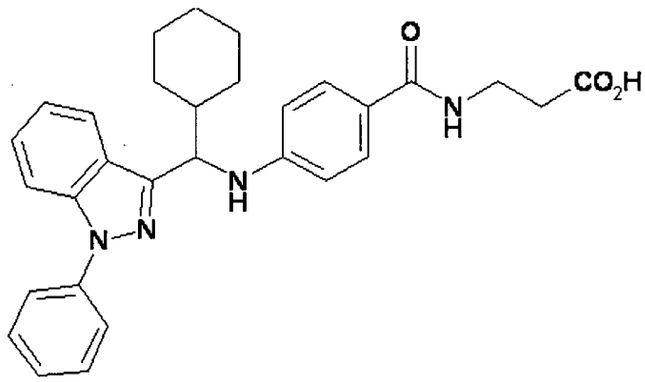
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,34 (m, 5 H), 1,53 - 1,87 (m, 5 H), 2,05 - 2,16 (m, 1 H), 2,45 (s, 3 H), 2,59 (t, J = 6,4 Hz, 2 H), 2,97 (s, 3 H), 3,65 (t, J = 6,4 Hz, 2 H), 4,53 (d, J = 7,5 Hz, 1 H), 6,50 (d, J = 8,7 Hz, 2 H), 7,18

1185

(d, J = 8,7 Hz, 2 H), 7,22 - 7,29 (m, 1 H), 7,30 - 7,38 (m, 1 H), 7,63 (d, J = 7,5 Hz, 1 H), 7,70 (d, J = 7,7 Hz, 1 H).

Ejemplo A14

Ácido 3-{[(4-{[ciclohexil(1-fenil-1H-indazol-3-il)metil]amino}fenil)carbonil]amino}propanoico




(1) 1-fenil-1H-indazol-3-carboxilato de metilo

A una mezcla de 1H-indazol-3-carboxilato de metilo (3,44 g), ácido fenilborónico (4,76 g), piridina (2,84 mL) y N,N-dimetilformamida (70 mL) se añadió acetato de cobre (II) (5,32 g) y la mezcla se agitó a 30 °C durante la noche. El material insoluble se filtró, se añadió solución acuosa saturada de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se lavó con carbonato de sodio saturado y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (1,58 g, 32%) en forma de un aceite amarillo pálido.

1186

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 4,07 (s, 3 H), 7,35 - 7,60 (m, 5 H), 7,70 - 7,77 (m, 3 H), 8,30 - 8,35 (m, 1 H).

(2) 1-fenil-1H-indazol-3-carbaldehído

A una solución (40 mL) de 1-fenil-1H-indazol-3-carboxilato de metilo (2,25 g) sintetizado con anterioridad en tetrahidrofurano se añadió gota a gota solución toluénica 1,5 M de hidruro de diisobutilaluminio (26,7 mL) a 0 °C y la mezcla se agitó durante 1 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite incoloro. A una solución del aceite obtenido en tetrahidrofurano (40 mL) se añadió dióxido de manganeso activo (8,00 g) y la mezcla se agitó a 50 °C durante 5 h. Adicionalmente se añadió dióxido de manganeso activo (1,00 g) y la mezcla se agitó a 50 °C durante 1 h. El dióxido de manganeso se filtró y el filtrado se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 3:17, relación en volumen) para dar el compuesto objeto del título (926 mg, 47%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 7,39 - 7,47 (m, 1 H), 7,47 - 7,55 (m, 2 H), 7,57 - 7,64 (m, 2 H), 7,72 - 7,80 (m, 3 H), 8,37 - 8,42 (m, 1 H), 10,34 (s, 1 H).

(3) ciclohexil(1-fenil-1H-indazol-3-il)metanol

Usando 1-fenil-1H-indazol-3-carbaldehído (926 mg) sintetizado con anterioridad y de la misma manera que en el

1187

Ejemplo A1(1), se obtuvo el compuesto objeto del título (716 mg, 56%) en forma de un aceite de color amarillo pálido. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,11 - 1,31 (m, 5 H), 1,51 - 1,84 (m, 4 H), 1,94 - 2,08 (m, 2 H), 2,52 (d, J = 4,5 Hz, 1 H), 4,93 - 5,00 (m, 1 H), 7,18 - 7,25 (m, 1 H), 7,31 - 7,38 (m, 1 H), 7,39 - 7,45 (m, 1 H), 7,49 - 7,56 (m, 2 H), 7,68 - 7,74 (m, 3 H), 7,87 - 7,92 (m, 1 H).

(4) 3-[cloro(ciclohexil)metil]-1-fenil-1H-indazol

A una mezcla de ciclohexil(1-fenil-1H-indazol-3-il)metanol (716 mg) sintetizado con anterioridad, piridina (284 µL) y tolueno (20 mL) se añadió cloruro de tionilo (256 µL) y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (767 mg, cuantitativo) en forma de un aceite amarillo pálido. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,99 - 1,38 (m, 5 H), 1,46 - 1,55 (m, 1 H), 1,60 - 1,72 (m, 2 H), 1,80 - 1,90 (m, 1 H), 2,24 - 2,44 (m, 2 H), 5,15 (d, J = 9,0 Hz, 1 H), 7,21 - 7,27 (m, 1 H), 7,32 - 7,39 (m, 1 H), 7,40 - 7,46 (m, 1 H), 7,49 - 7,56 (m, 2 H), 7,67 - 7,74 (m, 3 H), 7,96 - 8,00 (m, 1 H).

(5) ácido 3-{[(4-{[ciclohexil(1-fenil-1H-indazol-3-il)metil]amino}fenil)carbonil]amino}propanoico

Usando 3-[cloro(ciclohexil)metil]-1-fenil-1H-indazol (370 mg) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (269 mg)

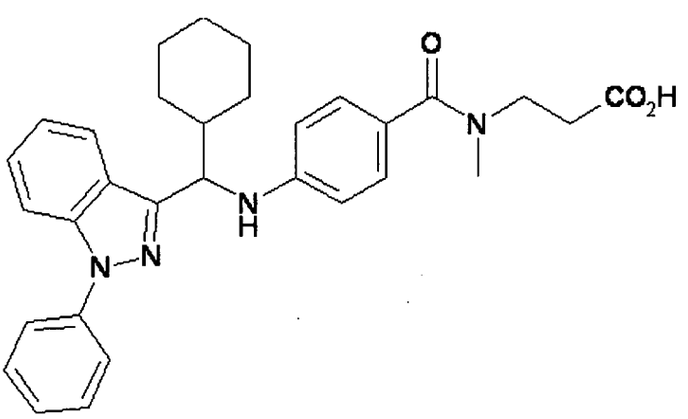
1188

sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo A7(3), se obtuvo el compuesto objeto del título (79,1 mg, 14%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,01 - 1,36 (m, 5 H), 1,54 - 1,84 (m, 4 H), 1,98 - 2,13 (m, 2 H), 2,52 - 2,64 (m, 2 H), 3,53 - 3,66 (m, 2 H), 4,81 (d, J = 6,8 Hz, 1 H), 6,52 - 6,71 (m, 3 H), 7,16 (t, J = 7,6 Hz, 1 H), 7,29 - 7,42 (m, 2 H), 7,45 - 7,56 (m, 4 H), 7,62 - 7,71 (m, 3 H), 7,81 (d, J = 8,3 Hz, 1 H).

Ejemplo A15

Ácido 3-{[(4-{[ciclohexil(1-fenil-1H-indazol-3-il)metil]amino}fenil)carbonil](metil)amino}propanoico



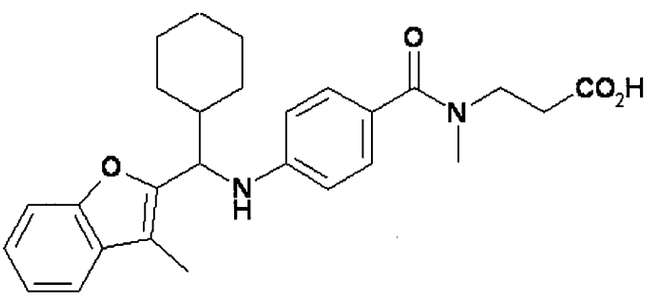

Usando 3-[cloro(ciclohexil)metil]-1-fenil-1H-indazol (397 mg) sintetizado en el Ejemplo A14(4) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (305 mg) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo A7(3), se obtuvo el compuesto objeto del título (76,9 mg, 12%) en forma de un sólido amarillo pálido.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,04 - 1,35 (m, 5 H), 1,54 - 1,84 (m, 4 H), 1,98 - 2,13 (m, 2 H), 2,56 - 2,67 (m, 2 H), 2,99 (s, 3 H), 3,67 (t, J = 6,1 Hz, 2 H), 4,80 (d, J = 6,4 Hz, 1 H), 6,66 (d, J = 8,7 Hz, 2 H), 7,13 - 7,18 (m, 1 H), 7,21 (d, J = 8,7 Hz, 2 H), 7,30 - 7,42 (m, 2 H), 7,52 (t, J = 7,8 Hz, 2 H), 7,64 - 7,72 (m, 2 H), 7,82 (d, J = 8,3 Hz, 1 H).

Ejemplo A16

Ácido 3-{[(4-{[ciclohexil(3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) 3-metil-1-benzofuran-2-carbaldehído

A una solución (40 mL) de 3-metil-1-benzofuran-2-carboxilato de etilo (2,00 g) en tetrahidrofurano se añadió gota a gota solución toluénica 1,5 M de hidruro de diisobutilaluminio (19,6 mL) a 0 °C y la mezcla se agitó durante 2 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido blanco. A una solución (40 mL) del sólido obtenido en

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diclorometano se añadió peryodinano de Dess-Martin (4,96 g) a 0 °C y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió solución acuosa saturada de sulfito de sodio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:9, relación en volumen) para dar el compuesto objeto del título (753 mg, 48%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,63 (s, 3 H), 7,30 - 7,37 (m, 1 H), 7,48 - 7,58 (m, 2 H), 7,67 - 7,71 (m, 1 H), 10,03 (s, 1 H).

(2) ciclohexil(3-metil-1-benzofuran-2-il)metanol

Usando 3-metil-1-benzofuran-2-carbaldehído (753 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(1), se obtuvo el compuesto objeto del título (843 mg, 73%) en forma de un aceite de color amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 - 1,03 (m, 1 H), 1,03 - 1,34 (m, 4 H), 1,34 - 1,44 (m, 1 H), 1,60 - 1,71 (m, 2 H), 1,75 - 1,99 (m, 3 H), 2,10 - 2,20 (m, 1 H), 2,23 (s, 3 H), 4,49 - 4,56 (m, 1 H), 7,18 - 7,29 (m, 2 H), 7,39 - 7,49 (m, 2 H).

(3) 2-[cloro(ciclohexil)metil]-3-metil-1-benzofurano

A una mezcla de ciclohexil(3-metil-1-benzofuran-2-il)metanol (843 mg) sintetizado con anterioridad y tolueno (20 mL) se añadió cloruro de tionilo (256 µL) y la mezcla se

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agitó a temperatura ambiente durante 2,5 h y a 50 °C durante 1,5 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (862 mg, 95%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 - 0,98 (m, 1 H), 1,00 - 1,37 (m, 4 H), 1,42 - 1,53 (m, 1 H), 1,57 - 1,77 (m, 2 H), 1,77 - 1,88 (m, 1 H), 2,12 - 2,28 (m, 4 H), 2,08 - 2,38 (m, 1 H), 4,82 (d, J = 9,6 Hz, 1 H), 7,14 - 7,33 (m, 2 H), 7,43 - 7,50 (m, 2 H).

(4) ácido 3-{[(4-{[ciclohexil(3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

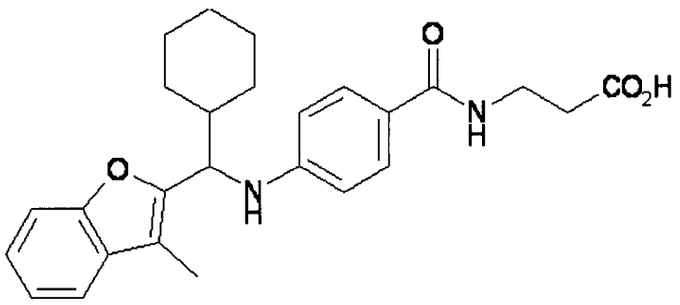
Usando 2-[cloro(ciclohexil)metil]-3-metil-1-benzofurano (429 mg) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (408 mg) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo A7(3), se obtuvo el compuesto objeto del título (247 mg, 34%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,37 (m, 5 H), 1,47 - 1,58 (m, 1 H), 1,60 - 1,73 (m, 2 H), 1,73 - 1,83 (m, 1 H), 1,84 - 1,98 (m, 1 H), 2,03 - 2,15 (m, 1 H), 2,25 (s, 3 H), 2,59 - 2,69 (m, 2 H), 3,01 (s, 2 H), 3,68 (t, J = 6,5 Hz, 2 H), 4,38 (d, J = 7,9 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 7,16 - 7,27 (m, 4 H), 7,35 - 7,40 (m, 1 H), 7,41 - 7,45 (m, 1 H).

Ejemplo A17

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Ácido 3-{[(4-{[ciclohexil(3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico



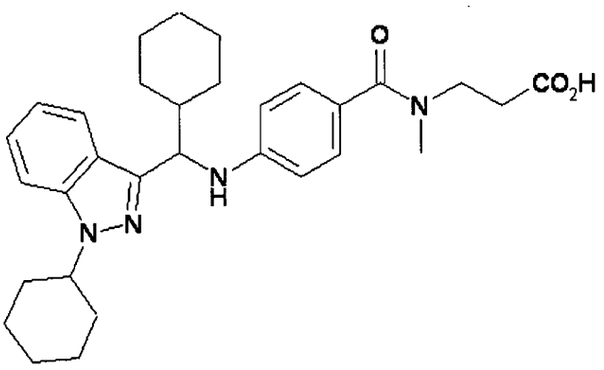
Usando 2-[cloro(ciclohexil)metil]-3-metil-1-benzofurano (433 mg) sintetizado en el Ejemplo A16(3) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (390 mg) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo A7(3), se obtuvo el compuesto objeto del título (268 mg, 37%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,37 (m, 5 H), 1,46 - 1,59 (m, 1 H), 1,59 - 1,74 (m, 2 H), 1,74 - 1,84 (m, 1 H), 1,84 - 1,99 (m, 1 H), 2,02 - 2,13 (m, 1 H), 2,25 (s, 3 H), 2,55 - 2,66 (m, 2 H), 3,57 - 3,68 (m, 2 H), 4,40 (d, J = 8,1 Hz, 1 H), 6,51 - 6,65 (m, 3 H), 7,14 - 7,25 (m, 2 H), 7,34 - 7,39 (m, 1 H), 7,39 - 7,45 (m, 1 H), 7,52 (d, J = 8,9 Hz, 2 H).

Ejemplo A18

Ácido 3-{[(4-{[ciclohexil(1-ciclohexil-1H-indazol-3-il)metil]amino}fenil)carbonil](metil)amino}propanoico

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(1) 1-ciclohexil-1H-indazol-3-carboxilato de metilo

A una mezcla de 1H-indazol-3-carboxilato de metilo (5,00 g), ciclohexanol (9,00 mL), trifenilfosfina (14,9 g) y tetrahidrofurano (100 mL) se añadió solución toluénica al 40% de azodicarboxilato de etilo (25,6 mL) y la mezcla se agitó durante la noche a temperatura ambiente. La mezcla de reacción se concentró a presión reducida, se añadió éter dietílico al residuo y la mezcla se agitó a 0 °C. El precipitado se filtró y el filtrado se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:9, relación en volumen) para dar el compuesto objeto del título (6,84 g, 93%) en forma de un aceite de color rojo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,25 - 1,43 (m, 1 H), 1,45 - 1,62 (m, 2 H), 1,72 - 1,82 (m, 1 H), 1,90 - 2,00 (m, 2 H), 2,01 - 2,16 (m, 4 H), 4,03 (s, 3 H), 5,50 - 5,62 (m, 1 H), 7,24 - 7,37 (m, 2 H), 7,78 - 7,83 (m, 1 H), 7,99 - 8,04 (m, 1 H).

(2) 1-ciclohexil-1H-indazol-3-carbaldehído

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Usando 1-ciclohexil-1H-indazol-3-carboxilato de metilo (3,08 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A14(2), se obtuvo el compuesto objeto del título (1,98 g, 73%) en forma de un aceite de color amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,31 - 1,43 (m, 1 H), 1,45 - 1,63 (m, 2 H), 1,74 - 1,84 (m, 1 H), 1,92 - 2,02 (m, 2 H), 2,06 - 2,18 (m, 4 H), 5,24 - 5,36 (m, 1 H), 7,33 - 7,43 (m, 2 H), 7,83 - 7,90 (m, 1 H), 7,98 - 8,05 (m, 1 H), 10,32 (s, 1 H).

(3) ciclohexil(1-ciclohexil-1H-indazol-3-il)metanol

Usando 1-ciclohexil-1H-indazol-3-carbaldehído (980 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(1), se obtuvo el compuesto objeto del título (984 mg, 73%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,82 - 1,00 (m, 1 H), 1,05 - 2,07 (m, 17 H), 2,07 - 2,33 (m, 4 H), 4,48 - 4,62 (m, 1 H), 4,93 (dd, J = 8,9, 3,6 Hz, 1 H), 6,99 - 7,07 (m, 1 H), 7,20 - 7,28 (m, 1 H), 7,65 - 7,73 (m, 2 H).

(4) 3-[cloro(ciclohexil)metil]-1-ciclohexil-1H-indazol

Usando ciclohexil(1-ciclohexil-1H-indazol-3-il)metanol (934 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A14(4), se obtuvo el compuesto objeto del título (1,05 g, cuantitativo) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,75 - 0,89 (m, 1 H), 1,06 - 2,08 (m, 16 H), 2,09 - 2,38 (m, 3 H), 2,45 - 2,56 (m, 1 H),

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4,41 - 4,54 (m, 1 H), 5,09 (d, J = 10,5 Hz, 1 H), 7,04 - 7,11 (m, 1 H), 7,21 - 7,29 (m, 1 H), 7,66 - 7,72 (m, 2 H).

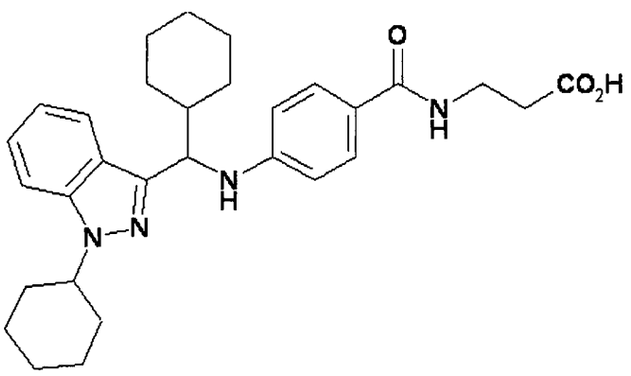
(5) ácido 3-{[(4-{[ciclohexil(1-ciclohexil-1H-indazol-3-il)metil]amino}fenil)carbonil](metil)amino}propanoico

Usando 3-[cloro(ciclohexil)metil]-1-ciclohexil-1H-indazol (400 mg) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (303 mg) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo A7(3), se obtuvo el compuesto objeto del título (451 mg, 72%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,50 (m, 9 H), 1,61 - 2,04 (m, 9 H), 2,06 - 2,29 (m, 3 H), 2,57 - 2,69 (m, 2 H), 2,99 (s, 3 H), 3,67 (t, J = 6,2 Hz, 2 H), 4,43 - 4,57 (m, 1 H), 4,72 (d, J = 8,3 Hz, 1 H), 6,47 (d, J = 8,7 Hz, 2 H), 6,99 - 7,06 (m, 1 H), 7,17 (d, J = 8,7 Hz, 2 H), 7,20 - 7,29 (m, 1 H), 7,65 - 7,73 (m, 4 H).

Ejemplo A19

Ácido 3-{[(4-{[ciclohexil(1-ciclohexil-1H-indazol-3-il)metil]amino}fenil)carbonil]amino}propanoico



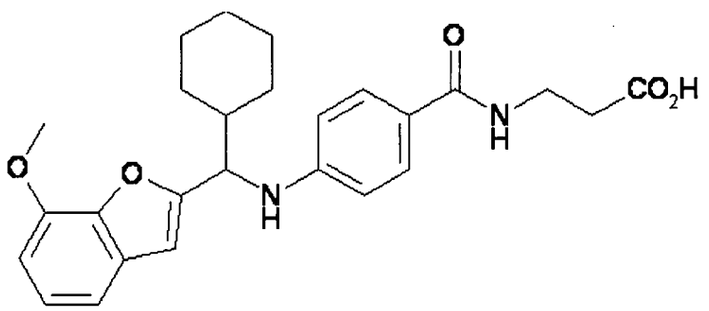
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Usando 3-[cloro(ciclohexil)metil]-1-ciclohexil-1H-indazol (400 mg) sintetizado en el Ejemplo A18(4) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (286 mg) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo A7(3), se obtuvo el compuesto objeto del título (441 mg, 72%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,48 (m, 9 H), 1,61 - 2,04 (m, 9 H), 2,03 - 2,29 (m, 3 H), 2,61 (t, J = 5,7 Hz, 2 H), 3,54 - 3,69 (m, 2 H), 4,43 - 4,55 (m, 1 H), 4,74 (d, J = 8,3 Hz, 1 H), 6,46 (d, J = 8,7 Hz, 2 H), 6,67 (t, J = 5,8 Hz, 1 H), 6,97 - 7,06 (m, 1 H), 7,18 - 7,29 (m, 1 H), 7,46 (d, J = 8,7 Hz, 2 H), 7,68 (d, J = 9,4 Hz, 2 H).

Ejemplo A20

Ácido 3-{[(4-{[ciclohexil(7-metoxi-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico




(1) 7-metoxi-1-benzofuran-2-carbaldehído

Usando 7-metoxi-1-benzofuran-2-carboxilato de etilo (2,00 g) y de la misma manera que en el Ejemplo A14(2), se obtuvo el compuesto objeto del título (950 mg, 59%) en forma de un aceite marrón.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 4,04 (s, 3 H), 6,96 - 7,00 (m, 1 H), 7,22 - 7,34 (m, 2 H), 7,54 (s, 1 H), 9,90 (s, 1 H).

(2) ciclohexil(7-metoxi-1-benzofuran-2-il)metanol

Usando 7-metoxi-1-benzofuran-2-carbaldehído (950 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(1), se obtuvo el compuesto objeto del título (790 mg, 56%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,34 (m, 5 H), 1,49 - 1,60 (m, 1 H), 1,60 - 1,83 (m, 3 H), 1,84 - 2,02 (m, 3 H), 4,00 (s, 3 H), 4,53 - 4,59 (m, 1 H), 6,60 (s, 1 H), 6,74 - 6,81 (m, 1 H), 7,09 - 7,17 (m, 2 H).

(3) 2-[cloro(ciclohexil)metil]-7-metoxi-1-benzofurano

Usando ciclohexil(7-metoxi-1-benzofuran-2-il)metanol (790 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(2), se obtuvo el compuesto objeto del título (823 mg, 97%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,37 (m, 5 H), 1,55 - 1,84 (m, 4 H), 2,06 - 2,25 (m, 2 H), 4,01 (s, 3 H), 4,81 (d, J = 7,8 Hz, 1 H), 6,67 (s, 1 H), 6,75 - 6,83 (m, 1 H), 7,10 - 7,18 (m, 2 H).

(4) ácido 3-{[(4-{[ciclohexil(7-metoxi-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico

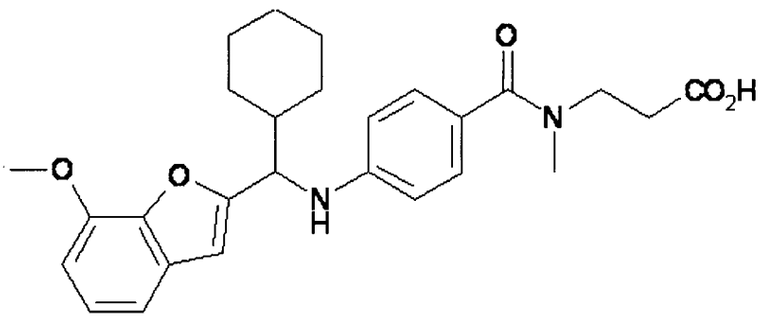
Usando 2-[cloro(ciclohexil)metil]-7-metoxi-1-benzofurano (422 mg) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (357 mg) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo A7(3), se obtuvo el compuesto objeto del título (64,3 mg, 9%) en forma de un sólido amarillo pálido.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,34 (m, 5 H), 1,54 - 1,82 (m, 4 H), 1,87 - 2,07 (m, 2 H), 2,64 (t, J = 5,6 Hz, 2 H), 3,59 - 3,69 (m, 2 H), 4,00 (s, 3 H), 4,43 (d, J = 6,4 Hz, 1 H), 6,50 (s, 1 H), 6,53 - 6,61 (m, 3 H), 6,75 (dd, J = 7,5, 1,3 Hz, 1 H), 7,02 - 7,13 (m, 2 H), 7,53 (d, J = 8,7 Hz, 2 H).

Ejemplo A21

Ácido 3-{[(4-{[ciclohexil(7-metoxi-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




Usando 2-[cloro(ciclohexil)metil]-7-metoxi-1-benzofurano (401 mg) sintetizado en el Ejemplo A20(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (360 mg) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo A7(3), se obtuvo el compuesto objeto del título (48,7 mg, 7%) en forma de un sólido blanco.

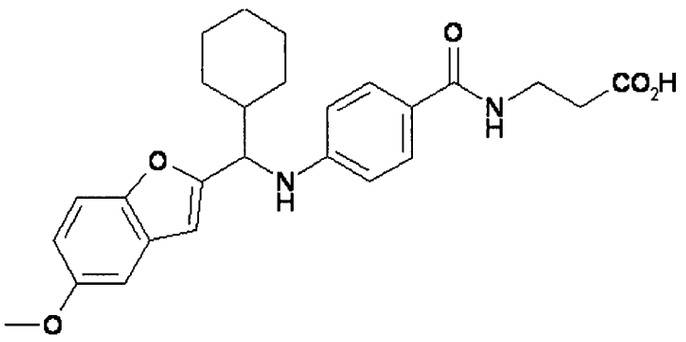
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 - 1,34 (m, 5 H), 1,54 - 1,82 (m, 4 H), 1,88 - 2,08 (m, 2 H), 2,68 (t, J = 6,4 Hz, 2 H), 3,04 (s, 3 H), 3,71 (t, J = 6,4 Hz, 2 H), 4,01 (s, 3 H), 4,42 (d, J = 6,6 Hz, 1 H), 6,51 (s, 1 H), 6,57 (d, J = 8,7

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Hz, 2 H), 6,76 (dd, J = 7,3, 1,5 Hz, 1 H), 7,04 - 7,15 (m, 2 H), 7,24 (d, J = 8,7 Hz, 2 H).

Ejemplo A22

Ácido 3-{[(4-{[ciclohexil(5-metoxi-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico



(1) 5-metoxi-1-benzofuran-2-carbaldehído

Usando 5-metoxi-1-benzofuran-2-carboxilato de etilo (2,00 g) y de la misma manera que en el Ejemplo A14(2), se obtuvo el compuesto objeto del título (914 mg, 57%) en forma de un sólido marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,86 (s, 3 H), 7,10 - 7,16 (m, 2 H), 7,46 - 7,52 (m, 2 H), 9,82 (s, 1 H).

(2) ciclohexil(5-metoxi-1-benzofuran-2-il)metanol

Usando 5-metoxi-1-benzofuran-2-carbaldehído (914 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(1), se obtuvo el compuesto objeto del título (702 mg, 52%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 - 1,35 (m, 5 H), 1,47 - 1,58 (m, 1 H), 1,60 - 2,02 (m, 6 H), 3,83 (s, 3 H), 4,47 -

1200

4,53 (m, 1 H), 6,54 (s, 1 H), 6,85 (dd, J = 8,7, 2,7 Hz, 1 H), 6,99 (d, J = 2,7 Hz, 1 H), 7,33 (d, J = 8,7 Hz, 1 H).

(3) 2-[cloro(ciclohexil)metil]-5-metoxi-1-benzofurano

Usando ciclohexil(5-metoxi-1-benzofuran-2-il)metanol (702 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(2), se obtuvo el compuesto objeto del título (722 mg, 96%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 - 1,38 (m, 5 H), 1,51 - 1,86 (m, 4 H), 2,06 - 2,21 (m, 2 H), 3,83 (s, 3 H), 4,75 (d, J = 8,1 Hz, 1 H), 6,59 - 6,61 (m, 1 H), 6,88 (dd, J = 8,9, 2,4 Hz, 1 H), 6,97 (d, J = 2,4 Hz, 1 H), 7,33 - 7,38 (m, 1 H).

(4) ácido 3-{[(4-{[ciclohexil(5-metoxi-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico

A una mezcla de 2-[cloro(ciclohexil)metil]-5-metoxi-1-benzofurano (360 mg) sintetizado con anterioridad, 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (305 mg) sintetizado en el Ejemplo 1(2), yoduro de sodio (291 mg) y N,N-dimetilacetamida (10 mL) se añadió carbonato de sodio (206 mg) y la mezcla se agitó a 80 °C durante la noche. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 11:9, relación en volumen) para dar un aceite amarillo. A una mezcla del aceite obtenido, tetrahidrofurano (2,5 mL) y etanol (2,5 mL) se añadió solución acuosa 1 N de

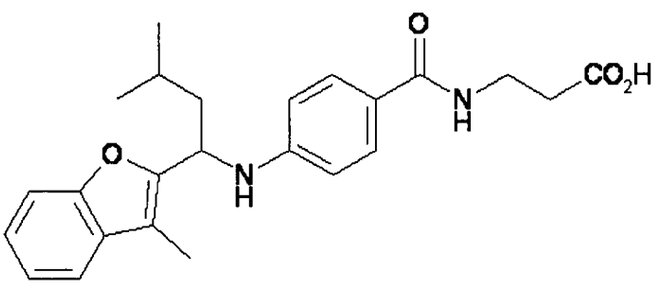
1201

hidróxido de sodio (1 mL) y la mezcla se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se concentró a presión reducida, el residuo se disolvió en agua (5 mL) y ácido clorhídrico 1 N (1 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (96,0 mg, 17%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,35 (m, 5 H), 1,54 - 1,84 (m, 4 H), 1,85 - 2,01 (m, 2 H), 2,60 - 2,69 (m, 2 H), 3,59 - 3,70 (m, 2 H), 3,80 (s, 3 H), 4,38 (d, J = 6,4 Hz, 1 H), 6,44 (s, 1 H), 6,53 - 6,62 (m, 3 H), 6,82 (dd, J = 9,1, 2,7 Hz, 1 H), 6,92 (d, J = 2,7 Hz, 1 H), 7,30 (d, J = 9,1 Hz, 1 H), 7,54 (d, J = 8,7 Hz, 2 H).

Ejemplo A23

Ácido 3-{[(4-{[3-metil-1-(3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil]amino}propanoico




(1) N-metoxi-N,3-dimetil-1-benzofuran-2-carboxamida

A una mezcla de ácido 3-metil-1-benzofuran-2-carboxílico (15,0 g), clorhidrato de N,O-dimetilhidroxiamina (9,95 g), monohidrato de 1-hidroxibenzotriazol (15,6 g), trietilamina

1202

(14,2 mL) y N,N-dimetilformamida (150 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (19,6 g) y la mezcla se agitó durante la noche a temperatura ambiente. Además, se añadieron clorhidrato de N,O-dimetilhidroxiamina (4,16 g), monohidrato de 1-hidroxibenzotriazol (6,52 g), trietilamina (5,94 mL) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (8,17 g) y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 3:7, relación en volumen) para dar el compuesto objeto del título (16,2 g, 87%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,51 (s, 3 H), 3,39 (s, 3 H), 3,87 (s, 3 H), 7,25 - 7,32 (m, 1 H), 7,37 - 7,50 (m, 2 H), 7,58 - 7,63 (m, 1 H).

(2) 3-metil-1-(3-metil-1-benzofuran-2-il)butan-1-ona

A una solución (20 mL) de N-metoxi-N,3-dimetil-1-benzofuran-2-carboxamida (1,00 g) sintetizada con anterioridad en tetrahidrofurano se añadió gota a gota una solución 1,0 M (6,84 mL) de bromuro de isobutilmagnesio en tetrahidrofurano a 0 °C y la mezcla se agitó durante 1 h. Además, se añadió solución 1,0 M de bromuro de isobutilmagnesio en tetrahidrofurano (6,84 mL) y la mezcla se

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agitó a 0 °C durante 1 h ten a temperatura ambiente durante 2 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:9, relación en volumen) para dar el compuesto objeto del título (873 mg, 89%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 (d, J = 6,9 Hz, 6 H), 2,26 - 2,41 (m, 1 H), 2,61 (s, 3 H), 2,87 (d, J = 6,9 Hz, 2 H), 7,26 - 7,33 (m, 1 H), 7,42 - 7,53 (m, 2 H), 7,62 - 7,67 (m, 1 H).

(3) 4-{[3-metil-1-(3-metil-1-benzofuran-2-il)butil]amino}benzoato de metilo

A una mezcla de 3-metil-1-(3-metil-1-benzofuran-2-il)butan-1-ona (200 mg) sintetizado con anterioridad, 4-aminobenzoato de metilo (140 mg), trietilamina (1,03 mL) y diclorometano (5 mL) se añadió cloruro de titanio (IV) (122 µL) a 0 °C y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido marrón oscuro. A una mezcla del sólido obtenido, se ácido acético (1 mL), metanol (5 mL) y tetrahidrofurano (5 mL) se añadió cianoborohidruro de sodio (175 mg) en pequeñas porciones y la

mezcla se agitó a temperatura ambiente durante 1 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (254 mg, 78%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 (d, J = 6,6 Hz, 3 H), 1,01 (d, J = 6,6 Hz, 3 H), 1,49 - 1,64 (m, 1 H), 1,79 - 1,96 (m, 2 H), 2,29 (s, 3 H), 3,81 (s, 3 H), 4,48 (d, J = 7,8 Hz, 1 H), 4,70 - 4,80 (m, 1 H), 6,58 (d, J = 8,9 Hz, 2 H), 7,16 - 7,26 (m, 2 H), 7,34 - 7,39 (m, 1 H), 7,41 - 7,45 (m, 1 H), 7,80 (d, J = 8,9 Hz, 2 H).

(4) ácido 4-{[3-metil-1-(3-metil-1-benzofuran-2-il)butil]amino}benzoico

A una mezcla de 4-{[3-metil-1-(3-metil-1-benzofuran-2-il)butil]amino}benzoato de metilo (1,38 g) sintetizado con anterioridad, tetrahidrofurano (20 mL) y etanol (20 mL) se añadió solución acuosa 1 N de hidróxido de sodio (20 mL) y la mezcla se agitó con calentamiento a reflujo durante la noche. Además, se añadió solución acuosa 1 N de hidróxido de sodio (20 mL) y la mezcla se agitó con calentamiento a reflujo durante 3 h. La mezcla de reacción se concentró a presión reducida, el ácido clorhídrico 1 N (40 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó sobre

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sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con éter diisopropílico para dar el compuesto objeto del título (1,06 g, 80%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 (d, J = 6,6 Hz, 3 H), 1,01 (d, J = 6,6 Hz, 3 H), 1,49 - 1,64 (m, 1 H), 1,79 - 1,97 (m, 2 H), 2,30 (s, 3 H), 4,77 (t, J = 7,5 Hz, 1 H), 6,59 (d, J = 9,0 Hz, 2 H), 7,16 - 7,28 (m, 2 H), 7,35 - 7,40 (m, 1 H), 7,42 - 7,47 (m, 1 H), 7,86 (d, J = 9,0 Hz, 2 H).

(5) ácido 3-{[(4-{[3-metil-1-(3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil]amino}propanoico

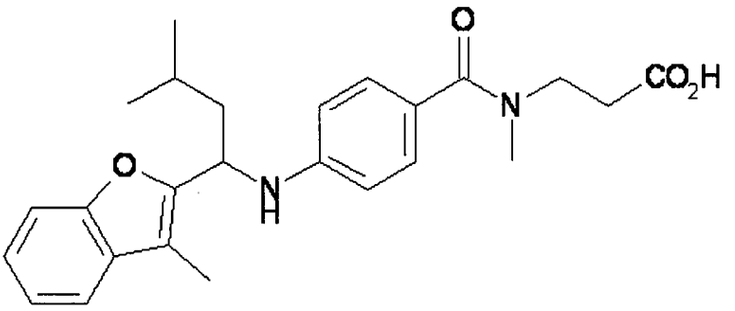
Usando ácido 4-{[3-metil-1-(3-metil-1-benzofuran-2-il)butil]amino}benzoico (300 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (289 mg, 80%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,6 Hz, 3 H), 1,00 (d, J = 6,6 Hz, 3 H), 1,48 - 1,64 (m, 1 H), 1,78 - 1,94 (m, 2 H), 2,28 (s, 3 H), 2,64 (t, J = 5,5 Hz, 2 H), 3,60 - 3,69 (m, 2 H), 4,73 (t, J = 7,5 Hz, 1 H), 6,54 - 6,65 (m, 3 H), 7,15 - 7,26 (m, 2 H), 7,34 - 7,39 (m, 1 H), 7,40 - 7,45 (m, 1 H), 7,54 (d, J = 8,7 Hz, 2 H).

Ejemplo A24

Ácido 3-{metil[(4-{[3-metil-1-(3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil]amino}propanoico

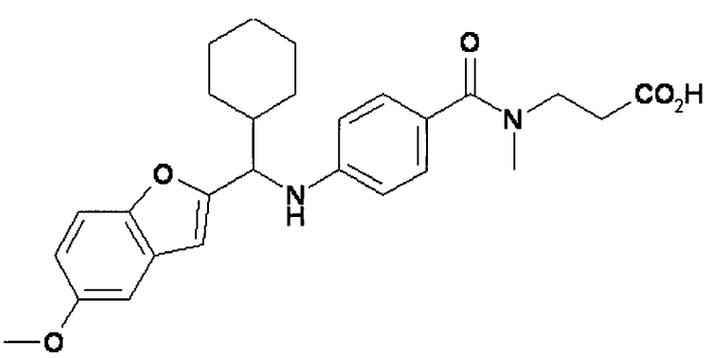
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Usando ácido 4-{[3-metil-1-(3-metil-1-benzofuran-2-il)butil]amino}benzoico (300 mg) sintetizado en el Ejemplo A23(4) y 3-(metilamino)propanoato de etilo (140 mg) y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (221 mg, 59%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,6 Hz, 3 H), 1,00 (d, J = 6,6 Hz, 3 H), 1,48 - 1,64 (m, 1 H), 1,81 - 1,92 (m, 2 H), 2,29 (s, 3 H), 2,61 - 2,71 (m, 2 H), 3,03 (s, 3 H), 3,70 (t, J = 6,4 Hz, 2 H), 4,71 (t, J = 7,5 Hz, 1 H), 6,58 (d, J = 8,5 Hz, 2 H), 7,16 - 7,29 (m, 6 H), 7,35 - 7,40 (m, 1 H), 7,41 - 7,46 (m, 1 H).

Ejemplo A25

Ácido 3-{[(4-{[ciclohexil(5-metoxi-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico



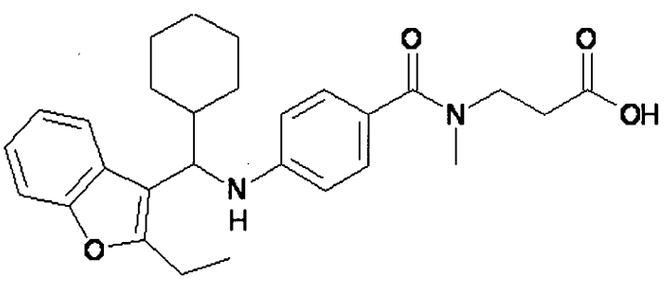
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Usando 2-[cloro(ciclohexil)metil]-5-metoxi-1-benzofurano (361 mg) sintetizado en el Ejemplo A22(3) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (325 mg) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo A22(4), se obtuvo el compuesto objeto del título (87,0 mg, 14%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,36 (m, 5 H), 1,55 - 1,84 (m, 4 H), 1,86 - 2,01 (m, 2 H), 2,61 - 2,74 (m, 2 H), 3,04 (s, 3 H), 3,71 (t, J = 6,2 Hz, 2 H), 3,81 (s, 3 H), 4,36 (d, J = 6,1 Hz, 1 H), 6,45 (s, 1 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,83 (dd, J = 8,9, 2,5 Hz, 1 H), 6,94 (d, J = 2,5 Hz, 1 H), 7,21 - 7,29 (m, 2 H), 7,31 (d, J = 8,9 Hz, 1 H).

Ejemplo A26

Ácido 3-{[(4-{[ciclohexil(2-etil-1-benzofuran-3-il)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) ciclohexil(2-etil-1-benzofuran-3-il)metanol

Usando 2-etil-1-benzofuran-3-carbaldehído (1,20 g) y de la misma manera que en el Ejemplo A1(1), se obtuvo el

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compuesto objeto del título (1,76 g, 99%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,79 - 0,94 (m, 1 H), 1,01 - 1,19 (m, 3 H), 1,20 - 1,34 (m, 4 H), 1,37 - 1,46 (m, 1 H), 1,57 - 1,70 (m, 2 H), 1,77 - 2,02 (m, 3 H), 2,17 - 2,27 (m, 1 H), 2,70 - 2,85 (m, 2 H), 4,54 (dd, J = 8,7, 2,7 Hz, 1 H), 7,14 - 7,24 (m, 2 H), 7,37 - 7,41 (m, 1 H), 7,60 - 7,65 (m, 1 H).

(2) 3-[cloro(ciclohexil)metil]-2-etil-1-benzofurano

Usando ciclohexil(2-etil-1-benzofuran-3-il)metanol (763 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(2), se obtuvo el compuesto objeto del título (765 mg, 94%) en forma de un aceite de color amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,75 - 0,89 (m, 1 H), 1,00 - 1,39 (m, 7 H), 1,43 - 1,53 (m, 1 H), 1,58 - 1,69 (m, 2 H), 1,78 - 1,89 (m, 1 H), 2,12 - 2,26 (m, 1 H), 2,35 - 2,46 (m, 1 H), 2,70 - 2,85 (m, 2 H), 4,78 (d, J = 9,9 Hz, 1 H), 7,14 - 7,28 (m, 2 H), 7,37 - 7,42 (m, 1 H), 7,67 - 7,72 (m, 1 H).

(3) ácido 3-{[(4-{[ciclohexil(2-etil-1-benzofuran-3-il)metil]amino}fenil)carbonil](metil)amino}propanoico

Usando 3-[cloro(ciclohexil)metil]-2-etil-1-benzofurano (300 mg) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (270 mg) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo A22(4), se obtuvo el compuesto objeto del título (287 mg, 57%) en forma de un sólido blanco.

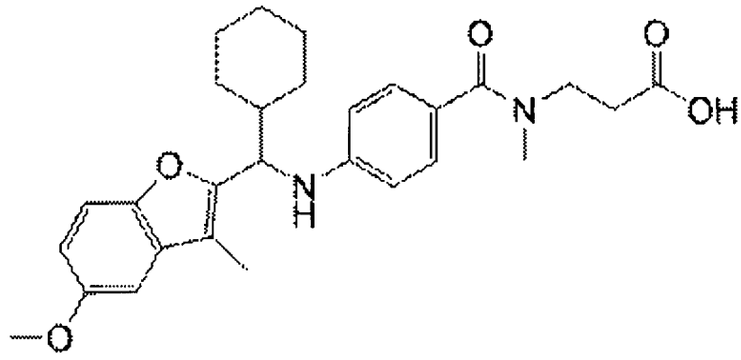
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,87 - 1,23 (m, 5 H), 1,28 (t, J = 7,5 Hz, 3 H), 1,55 - 1,75 (m, 3 H), 1,75 - 1,98 (m, 2 H),

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2,04 - 2,15 (m, 1 H), 2,61 - 2,71 (m, 2 H), 2,75 - 2,90 (m, 2 H), 3,02 (s, 3 H), 3,69 (t, J = 6,4 Hz, 2 H), 4,30 (d, J = 7,9 Hz, 1 H), 6,49 (d, J = 8,7 Hz, 2 H), 7,12 - 7,24 (m, 4 H), 7,35 - 7,41 (m, 1 H), 7,53 - 7,59 (m, 1 H).

Ejemplo A27

Ácido 3-{[(4-{[ciclohexil(5-metoxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico



(1) 5-metoxi-3-metil-1-benzofuran-2-carboxilato de metilo

A una mezcla de 1-(2-hidroxi-5-metoxifenil)etanona (5,00 g), bromoacetato de metilo (3,13 mL) y N,N-dimetilformamida (50 mL) se añadió carbonato de potasio (12,5 g) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió agua para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite marrón. A una solución (50 mL) del aceite obtenido en metanol se añadió metóxido de sodio (1,63 g) y la mezcla se agitó con calentamiento a reflujo durante 3 h. Se añadió ácido

1210

clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (1,25 g, 19%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,57 (s, 3 H), 3,87 (s, 3 H), 3,97 (s, 3 H), 6,99 (d, J = 2,6 Hz, 1 H), 7,06 (dd, J = 9,0, 2,6 Hz, 1 H), 7,42 (d, J = 9,0 Hz, 1 H).

(2) 5-metoxi-3-metil-1-benzofuran-2-carbaldehído

A una solución (100 mL) de 5-metoxi-3-metil-1-benzofuran-2-carboxilato de metilo (5,00 g) en tetrahidrofurano se añadió hidruro de litio y aluminio (862 mg) a 0 °C y la mezcla se agitó durante 1,5 h. Se añadió agua (860 µL) para neutralizar la reacción, una solución acuosa 1 N de hidróxido de sodio (860 µL) se agregó y la mezcla se agitó a temperatura ambiente durante 1 h. El material insoluble resultante se filtró y el filtrado se concentró a presión reducida para dar un sólido de color amarillo pálido. A una solución del sólido obtenido en tetrahidrofurano (80 mL) se añadió dióxido de manganeso activo (21,2 g) y la mezcla se agitó a 50 °C durante la noche. El dióxido de manganeso se filtró y el filtrado se concentró a presión reducida para dar el compuesto objeto del título (3,41 g, 79%) en forma de un sólido marrón.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,60 (s, 3 H), 3,88 (s, 3 H), 7,03 (d, J = 2,5 Hz, 1 H), 7,14 (dd, J = 9,0, 2,5 Hz, 1 H), 7,44 (d, J = 9,0 Hz, 1 H), 10,00 (s, 1 H).

(3) ciclohexil(5-metoxi-3-metil-1-benzofuran-2-il)metanol

Usando 5-metoxi-3-metil-1-benzofuran-2-carbaldehído (1,50 g) sintetizado con anterioridad as en el Ejemplo A1(1), se obtuvo el compuesto objeto del título (1,54 g, 71%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 - 0,99 (m, 1 H), 1,00 - 1,33 (m, 4 H), 1,33 - 1,44 (m, 1 H), 1,60 - 1,70 (m, 2 H), 1,74 - 1,99 (m, 3 H), 2,09 - 2,22 (m, 4 H), 3,85 (s, 3 H), 4,50 (dd, J = 8,6, 6,5 Hz, 1 H), 6,86 (dd, J = 8,7, 2,6 Hz, 1 H), 6,91 (d, J = 2,6 Hz, 1 H), 7,30 (d, J = 8,7 Hz, 1 H).

(4) 2-[cloro(ciclohexil)metil]-5-metoxi-3-metil-1-benzofurano

Usando ciclohexil(5-metoxi-3-metil-1-benzofuran-2-il)metanol (754 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(2), se obtuvo el compuesto objeto del título (795 mg, 99%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,83 - 0,97 (m, 1 H), 1,00 - 1,40 (m, 4 H), 1,42 - 1,52 (m, 1 H), 1,60 - 1,70 (m, 2 H), 1,77 - 1,87 (m, 1 H), 2,10 - 2,38 (m, 5 H), 3,85 (s, 3 H), 4,80 (d, J = 9,6 Hz, 1 H), 6,86 - 6,91 (m, 2 H), 7,31 - 7,36 (m, 1 H).

(5) ácido 3-{[(4-{[ciclohexil(5-metoxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

Usando 2-[cloro(ciclohexil)metil]-5-metoxi-3-metil-1-benzofurano (395 mg) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (338 mg)

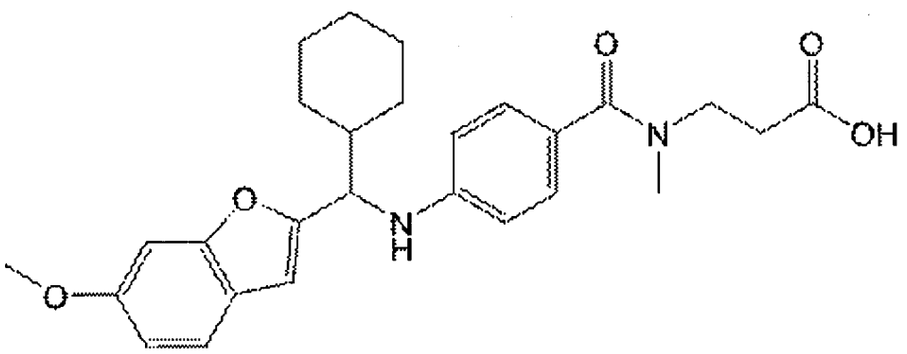
1212

sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo A22(4), se obtuvo el compuesto objeto del título (305 mg, 47%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,37 (m, 5 H), 1,47 - 1,57 (m, 1 H), 1,60 - 1,96 (m, 4 H), 2,03 - 2,13 (m, 1 H), 2,23 (s, 3 H), 2,65 (t, J = 6,4 Hz, 2 H), 3,02 (s, 3 H), 3,69 (t, J = 6,4 Hz, 2 H), 3,83 (s, 3 H), 4,36 (d, J = 8,0 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,82 (dd, J = 8,9, 2,4 Hz, 1 H), 6,88 (d, J = 2,4 Hz, 1 H), 7,19 - 7,29 (m, 3 H).

Ejemplo A28

Ácido 3-{[(4-{[ciclohexil(6-metoxi-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) 6-metoxi-1-benzofuran-2-carbonitrilo

A una mezcla de 2-hidroxi-4-metoxibenzaldehído (10,0 g), bromoacetonitrilo (5,04 mL) y acetona (100 mL) se añadió carbonato de potasio (18,1 g) y la mezcla se agitó a temperatura ambiente durante 3 h. El material insoluble se filtró y el filtrado se concentró a presión reducida para dar un sólido de color marrón pálido. A una solución (100 mL) del

sólido obtenido en N,N-dimetilformamida se añadió 1,8-diazabiciclo[5,4,0]undec-7-eno (9,83 mL) y la mezcla se agitó a 140 °C durante 1,5 h. La mezcla de reacción se concentró a presión reducida, ácido clorhídrico 1 N se añadió y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. Se añadió acetato de etilo al residuo, el material insoluble se filtró y el filtrado se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 3:17, relación en volumen) para dar el compuesto objeto del título (5,32 g, 47%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,88 (s, 3 H), 6,96 - 7,04 (m, 2 H), 7,39 (d, J = 0,9 Hz, 1 H), 7,52 (d, J = 8,5 Hz, 1 H).

(2)ciclohexil(6-metoxi-1-benzofuran-2-il)metanona

A una solución (20 mL) de 6-metoxi-1-benzofuran-2-carbonitrilo (1,00 g) sintetizado con anterioridad en tetrahidrofurano se añadió solución 1,0 M de bromuro de ciclohexilmagnesio en tetrahidrofurano (11,5 mL) y la mezcla se agitó a 50 °C durante la noche y se agitó con calentamiento a reflujo durante 1 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:9, relación en volumen) para dar

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el compuesto objeto del título (584 mg, 39%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,20 - 1,64 (m, 5 H), 1,69 - 1,79 (m, 1 H), 1,81 - 1,98 (m, 4 H), 3,09 - 3,21 (m, 1 H), 3,87 (s, 3 H), 6,93 (dd, J = 8,4, 2,1 Hz, 1 H), 7,03 - 7,06 (m, 1 H), 7,44 - 7,46 (m, 1 H), 7,54 (d, J = 8,4 Hz, 1 H).

(3) 4-{[ciclohexil(6-metoxi-1-benzofuran-2-il)metil]amino}benzoato de metilo

Usando ciclohexil(6-metoxi-1-benzofuran-2-il)metanona (584 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A23(3), se obtuvo el compuesto objeto del título (682 mg, 77%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 - 1,36 (m, 5 H), 1,56 - 1,84 (m, 4 H), 1,86 - 2,00 (m, 2 H), 3,81 (s, 3 H), 3,83 (s, 3 H), 4,35 - 4,57 (m, 2 H), 6,44 (s, 1 H), 6,58 (d, J = 8,9 Hz, 1 H), 6,81 (dd, J = 8,6, 2,3 Hz, 1 H), 6,97 (d, J = 2,3 Hz, 1 H), 7,31 (d, J = 8,6 Hz, 1 H), 7,80 (d, J = 8,9 Hz, 2 H).

(4) ácido 4-{[ciclohexil(6-metoxi-1-benzofuran-2-il)metil]amino}benzoico

Usando 4-{[ciclohexil(6-metoxi-1-benzofuran-2-il)metil]amino}benzoato de metilo (682 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A23(4), se obtuvo el compuesto objeto del título (633 mg, 96%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,37 (m, 5 H), 1,56 - 1,86 (m, 4 H), 1,86 - 2,01 (m, 2 H), 3,83 (s, 3 H), 4,36 - 4,46 (m, 1 H), 4,48 - 4,65 (m, 1 H), 6,45 (s, 1 H), 6,60 (d,

J = 8,9 Hz, 2 H), 6,82 (dd, J = 8,6, 2,3 Hz, 1 H), 6,98 (d, J = 2,3 Hz, 1 H), 7,33 (d, J = 8,6 Hz, 1 H), 7,86 (d, J = 8,9 Hz, 2 H).

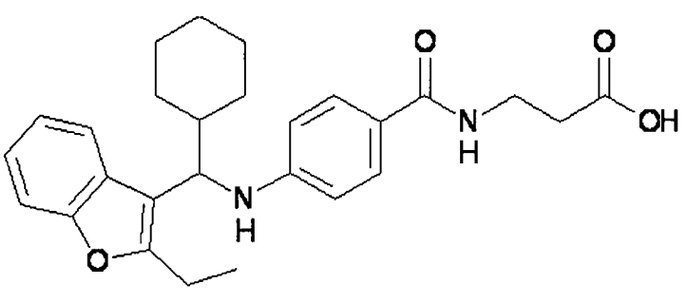
(5) ácido 3-{[(4-{[ciclohexil(6-metoxi-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

Usando ácido 4-{[ciclohexil(6-metoxi-1-benzofuran-2-il)metil]amino}benzoico (300 mg) sintetizado con anterioridad y 3-(metilamino)propanoato de etilo (125 mg) y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (201 mg, 55%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 - 1,36 (m, 5 H), 1,55 - 1,84 (m, 4 H), 1,85 - 2,00 (m, 2 H), 2,67 (t, J = 6,5 Hz, 2 H), 3,03 (s, 3 H), 3,70 (t, J = 6,5 Hz, 2 H), 3,83 (s, 3 H), 4,35 (d, J = 6,6 Hz, 1 H), 6,44 (s, 1 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,82 (dd, J = 8,5, 2,2 Hz, 1 H), 6,98 (d, J = 2,2 Hz, 1 H), 7,22 - 7,28 (m, 2 H), 7,32 (d, J = 8,5 Hz, 1 H).

Ejemplo A29

Ácido 3-{[(4-{[ciclohexil(2-etil-1-benzofuran-3-il)metil]amino}fenil)carbonil]amino}propanoico



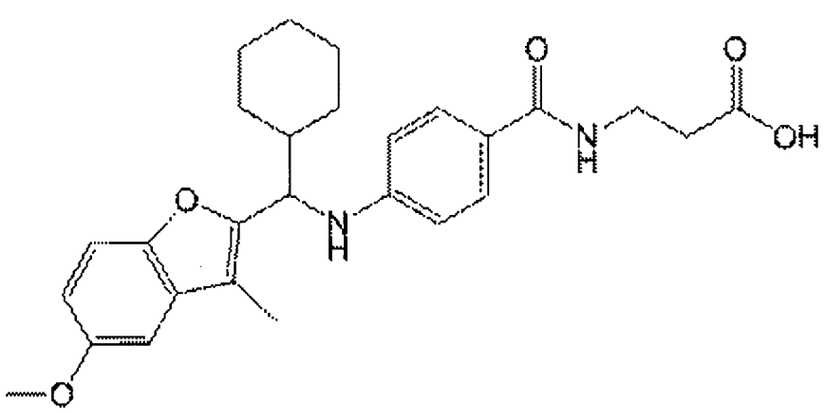
1216

Usando 3-[cloro(ciclohexil)metil]-2-etil-1-benzofurano (300 mg) sintetizado en el Ejemplo A26(2) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (255 mg) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo A22(4), se obtuvo el compuesto objeto del título (374 mg, 77%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,23 (m, 5 H), 1,27 (t, J = 7,5 Hz, 3 H), 1,55 - 1,74 (m, 3 H), 1,76 - 1,97 (m, 2 H), 2,04 - 2,15 (m, 1 H), 2,56 - 2,66 (m, 2 H), 2,71 - 2,92 (m, 2 H), 3,56 - 3,66 (m, 2 H), 4,31 (d, J = 7,9 Hz, 1 H), 6,48 (d, J = 8,7 Hz, 2 H), 6,52 - 6,62 (m, 1 H), 7,11 - 7,22 (m, 2 H), 7,34 - 7,40 (m, 1 H), 7,47 (d, J = 8,7 Hz, 2 H), 7,52 - 7,57 (m, 1 H).

Ejemplo A30

Ácido 3-{[(4-{[ciclohexil(5-metoxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico




Usando 2-[cloro(ciclohexil)metil]-5-metoxi-3-metil-1-benzofurano (395 mg) sintetizado en el Ejemplo A27(4) y 3-

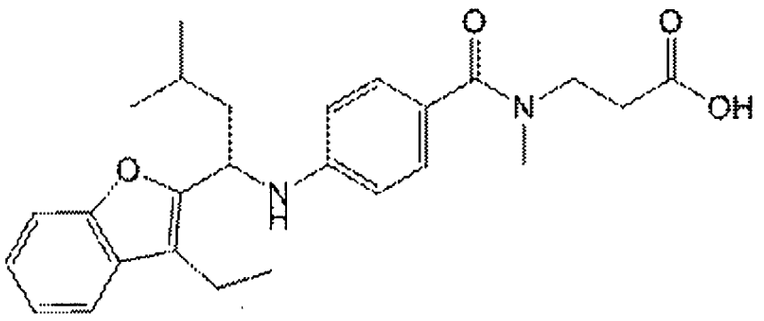
1217

{[(4-aminofenil)carbonil]amino}propanoato de etilo (319 mg) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo A22(4), se obtuvo el compuesto objeto del título (413 mg, 66%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,36 (m, 5 H), 1,46 - 1,58 (m, 1 H), 1,60 - 1,97 (m, 4 H), 2,01 - 2,13 (m, 1 H), 2,22 (s, 3 H), 2,61 (t, J = 5,9 Hz, 2 H), 3,57 - 3,67 (m, 2 H), 3,82 (s, 3 H), 4,37 (d, J = 8,0 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,61 (t, J = 6,1 Hz, 1 H), 6,81 (dd, J = 9,1, 2,7 Hz, 1 H), 6,87 (d, J = 2,3 Hz, 1 H), 7,21 - 7,28 (m, 1 H), 7,52 (d, J = 8,7 Hz, 2 H).

Ejemplo A31

Ácido 3-{[(4-{[1-(3-etil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil](metil)amino}propanoico




(1) 3-etil-1-benzofuran-2-carboxilato de metilo

A una mezcla de 1-(2-hidroxifenil)propan-1-ona (10,0 g), bromoacetato de metilo (5,11 mL) y acetona (100 mL) se añadió carbonato de potasio (18,4 g) y la mezcla se agitó durante la noche a temperatura ambiente. El material insoluble se filtró y el filtrado se concentró a presión reducida. El residuo se

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purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar un aceite incoloro. A una solución (150 mL) del aceite obtenido en N,N-dimetilformamida se añadió 1,8-diazabiciclo[5,4,0]undec-7-eno (8,12 mL) y la mezcla se agitó a 120 °C durante 2 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. Se añadió acetato de etilo al residuo, el material insoluble se filtró y el filtrado se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:9, relación en volumen) para dar el compuesto objeto del título (7,14 g, 52%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,31 (t, J = 7,5 Hz, 4 H), 3,12 (q, J = 7,5 Hz, 2 H), 3,99 (s, 3 H), 7,27 - 7,34 (m, 1 H), 7,41 - 7,49 (m, 1 H), 7,53 - 7,58 (m, 1 H), 7,65 - 7,70 (m, 1 H).

(2) 3-etil-1-benzofuran-2-carbaldehído

Usando 3-etil-1-benzofuran-2-carboxilato de metilo (3,00 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A27(2), se obtuvo el compuesto objeto del título (2,27 g, 90%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,40 (t, J = 7,6 Hz, 3 H), 3,12 (q, J = 7,6 Hz, 2 H), 7,30 - 7,37 (m, 1 H), 7,48 - 7,60 (m, 2 H), 7,71 - 7,76 (m, 1 H), 10,04 (s, 1 H).

(3) 1-(3-etil-1-benzofuran-2-il)-3-metilbutan-1-ol

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A una solución (50 mL) de 3-etil-1-benzofuran-2-carbaldehído (2,27 g) sintetizada con anterioridad en tetrahidrofurano se añadió gota a gota solución 1,0 M de bromuro de isobutilmagnesio en tetrahidrofurano (19,5 mL) a 0 °C y la mezcla se agitó durante 1 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 3:17, relación en volumen) para dar el compuesto objeto del título (1,55 g, 51%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 (d, J = 6,6 Hz, 3 H), 0,96 (d, J = 6,6 Hz, 3 H), 1,28 (t, J = 7,5 Hz, 3 H), 1,56 - 1,73 (m, 1 H), 1,74 - 1,86 (m, 2 H), 1,88 - 1,99 (m, 1 H), 2,74 (q, J = 7,5 Hz, 2 H), 4,91 - 4,99 (m, 1 H), 7,18 - 7,31 (m, 2 H), 7,41 - 7,47 (m, 1 H), 7,50 - 7,56 (m, 1 H).

(4) 2-(1-cloro-3-metilbutil)-3-etil-1-benzofurano

Usando 1-(3-etil-1-benzofuran-2-il)-3-metilbutan-1-ol (1,00 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(2), se obtuvo el compuesto objeto del título (1,03 g, 96%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 0,97 (m, 6 H), 1,29 (t, J = 7,5 Hz, 3 H), 1,60 - 1,75 (m, 1 H), 2,14 - 2,21 (m, 2 H), 2,73 (q, J = 7,5 Hz, 2 H), 5,22 (t, J = 8,0 Hz, 1 H), 7,19 - 7,33 (m, 2 H), 7,41 - 7,48 (m, 1 H), 7,51 - 7,55 (m, 1 H).

1220

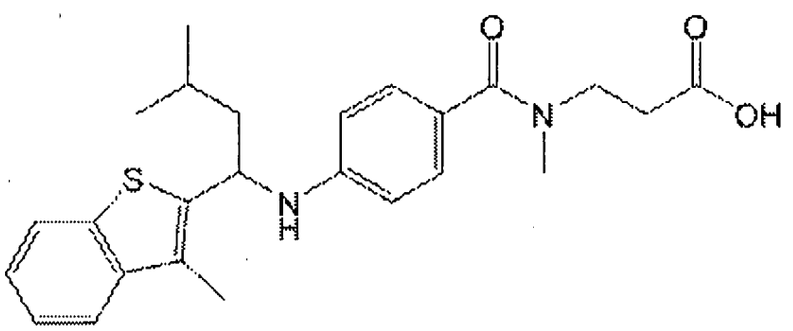
(5) ácido 3-{[(4-{[1-(3-etil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil](metil)amino}propanoico

Usando 2-(1-cloro-3-metilbutil)-3-etil-1-benzofurano (300 mg) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (300 mg) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo A22(4), se obtuvo el compuesto objeto del título (97,4 mg, 19%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 (d, J = 6,6 Hz, 3 H), 1,00 (d, J = 6,4 Hz, 3 H), 1,27 (t, J = 7,6 Hz, 3 H), 1,51 - 1,69 (m, 1 H), 1,82 - 1,89 (m, 2 H), 2,60 - 2,70 (m, 2 H), 2,77 (q, J = 7,6 Hz, 2 H), 3,02 (s, 3 H), 3,69 (t, J = 6,4 Hz, 2 H), 4,72 (t, J = 7,5 Hz, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 7,15 - 7,28 (m, 4 H), 7,36 - 7,42 (m, 1 H), 7,47 - 7,52 (m, 1 H).

Ejemplo A32

Ácido 3-{metil[(4-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}fenil)carbonil]amino}propanoico




(1) 3-metil-1-(3-metil-1-benzotiofen-2-il)butan-1-ona

A una mezcla de 3-metil-1-benzotiofeno (5,00 g), cloruro de isovalerilo (4,52 mL) y nitrometano (50 mL) se añadió

cloruro de aluminio (III) (8,98 g) a 0 °C y la mezcla se agitó a 0 °C durante 30 min, luego a temperatura ambiente durante 4 h. La mezcla de reacción se vertió en agua helada y la mezcla se extrajo con acetato de etilo. El extracto se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:19, relación en volumen) para dar el compuesto objeto del título (7,72 g, 99%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 (d, J = 6,8 Hz, 6 H), 2,28 - 2,43 (m, 1 H), 2,77 (s, 3 H), 2,80 (d, J = 7,0 Hz, 2 H), 7,39 - 7,53 (m, 2 H), 7,81 - 7,90 (m, 2 H).

(2) 4-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}benzoato de metilo

Usando 3-metil-1-(3-metil-1-benzotiofen-2-il)butan-1-ona (1,00 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A23(3), se obtuvo el compuesto objeto del título (923 mg, 58%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 (d, J = 6,0 Hz, 3 H), 1,02 (d, J = 6,0 Hz, 3 H), 1,68 - 1,81 (m, 2 H), 1,81 - 1,95 (m, 1 H), 2,47 (s, 3 H), 3,80 (s, 3 H), 4,40 - 4,47 (m, 1 H), 4,86 - 4,95 (m, 1 H), 6,54 (d, J = 8,1 Hz, 2 H), 7,23 - 7,30 (m, 1 H), 7,32 - 7,39 (m, 1 H), 7,62 - 7,67 (m, 2 H), 7,69 - 7,74 (m, 1 H), 7,79 (d, J = 8,1 Hz, 2 H).

(3) ácido 4-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}benzoico

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Usando 4-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}benzoato de metilo (923 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A23(4), se obtuvo el compuesto objeto del título (817 mg, 92%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 (d, J = 6,2 Hz, 3 H), 1,02 (d, J = 6,2 Hz, 3 H), 1,67 - 1,96 (m, 3 H), 2,47 (s, 3 H), 4,88 - 4,96 (m, 1 H), 6,55 (d, J = 8,9 Hz, 2 H), 7,23 - 7,30 (m, 1 H), 7,32 - 7,39 (m, 1 H), 7,62 - 7,68 (m, 1 H), 7,69 - 7,74 (m, 1 H), 7,84 (d, J = 8,9 Hz, 2 H).

(4) ácido 3-{metil[(4-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}fenil)carbonil]amino}propanoico

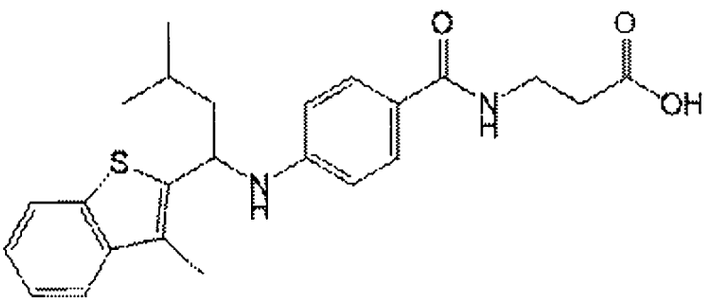
Usando ácido 4-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}benzoico (300 mg) sintetizado con anterioridad y 3-(metilamino)propanoato de etilo (134 mg) y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (218 mg, 59%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 (d, J = 6,2 Hz, 3 H), 1,02 (d, J = 6,2 Hz, 3 H), 1,66 - 1,94 (m, 3 H), 2,46 (s, 3 H), 2,62 - 2,72 (m, 2 H), 3,02 (s, 3 H), 3,70 (t, J = 6,4 Hz, 2 H), 4,82 - 4,89 (m, 1 H), 6,54 (d, J = 8,7 Hz, 2 H), 7,20 - 7,31 (m, 3 H), 7,32 - 7,39 (m, 1 H), 7,65 (d, J = 7,9 Hz, 1 H), 7,72 (d, J = 7,3 Hz, 1 H).

Ejemplo A33

Ácido 3-{[(4-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}fenil)carbonil]amino}propanoico

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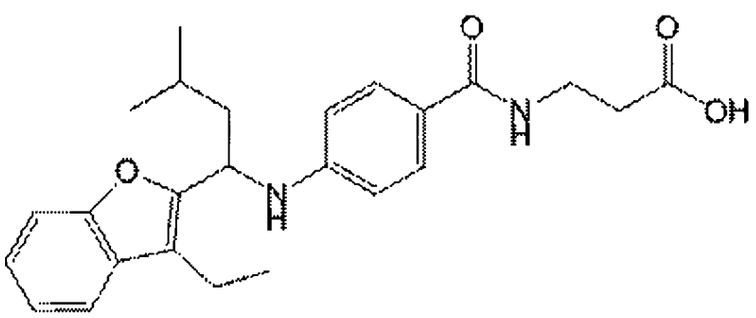


Usando ácido 4-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}benzoico (300 mg) sintetizado en el Ejemplo A32(3) y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (316 mg, 88%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 (d, J = 6,0 Hz, 3 H), 1,01 (d, J = 6,2 Hz, 3 H), 1,66 - 1,94 (m, 3 H), 2,46 (s, 3 H), 2,61 (t, J = 5,7 Hz, 2 H), 3,57 - 3,67 (m, 2 H), 4,83 - 4,91 (m, 1 H), 6,50 - 6,62 (m, 3 H), 7,22 - 7,29 (m, 1 H), 7,31 - 7,38 (m, 1 H), 7,51 (d, J = 8,7 Hz, 2 H), 7,64 (d, J = 7,5 Hz, 1 H), 7,70 (d, J = 7,9 Hz, 1 H).

Ejemplo A34

Ácido 3-{[(4-{[1-(3-etil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil]amino}propanoico



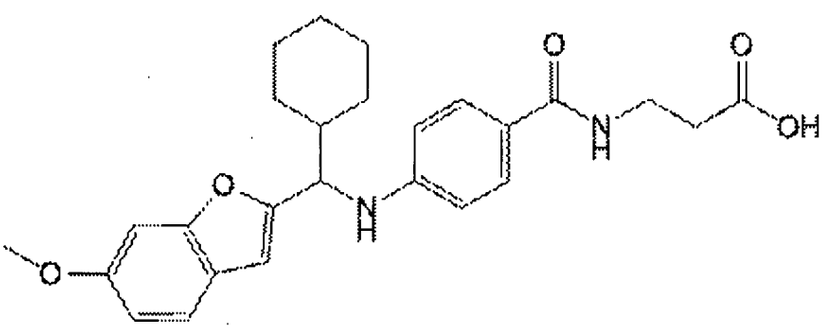
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Usando 2-(1-cloro-3-metilbutil)-3-etil-1-benzofurano (300 mg) sintetizado en el Ejemplo A31(4) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (283 mg) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo A22(4), se obtuvo el compuesto objeto del título (162 mg, 32%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,6 Hz, 3 H), 1,00 (d, J = 6,6 Hz, 3 H), 1,27 (t, J = 7,5 Hz, 3 H), 1,51 - 1,68 (m, 1 H), 1,81 - 1,90 (m, 2 H), 2,58 - 2,68 (m, 2 H), 2,76 (q, J = 7,5 Hz, 2 H), 3,58 - 3,68 (m, 2 H), 4,73 (t, J = 7,5 Hz, 1 H), 6,54 - 6,63 (m, 3 H), 7,14 - 7,26 (m, 2 H), 7,35 - 7,40 (m, 1 H), 7,46 - 7,51 (m, 1 H), 7,54 (d, J = 8,7 Hz, 2 H).

Ejemplo A35

Ácido 3-{[(4-{[ciclohexil(6-metoxi-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico




Usando ácido 4-{[ciclohexil(6-metoxi-1-benzofuran-2-il)metil]amino}benzoico (102 mg) sintetizado en el Ejemplo A28(4) y de la misma manera que en el Ejemplo A1(4), se

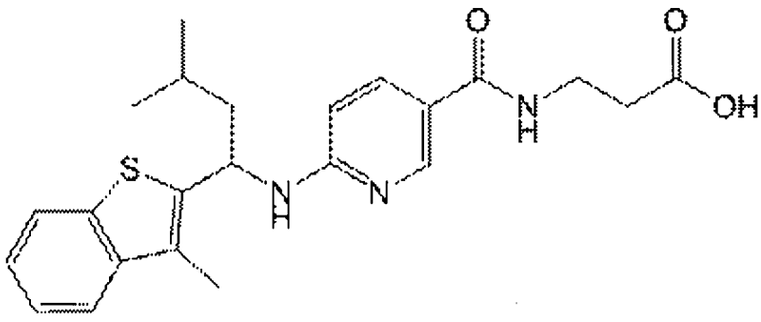
1225

obtuvo el compuesto objeto del título (40,0 mg, 33%) en forma de un sólido de color rojo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 1,35 (m, 5 H), 1,54 - 1,84 (m, 4 H), 1,84 - 1,99 (m, 2 H), 2,55 - 2,68 (m, 2 H), 3,56 - 3,69 (m, 2 H), 3,82 (s, 3 H), 4,36 (d, J = 6,4 Hz, 1 H), 6,42 (s, 1 H), 6,51 - 6,66 (m, 3 H), 6,81 (dd, J = 8,5, 2,1 Hz, 1 H), 6,97 (d, J = 2,1 Hz, 1 H), 7,31 (d, J = 8,5 Hz, 1 H), 7,53 (d, J = 8,3 Hz, 2 H).

Ejemplo A36

Ácido 3-{[(6-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}piridin-3-il)carbonil]amino}propanoico




(1) 6-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}piridin-3-carboxilato de metilo

A una mezcla de 3-metil-1-(3-metil-1-benzotiofen-2-il)butan-1-ona (1,00 g) sintetizada en el Ejemplo A32(1), 6-aminopiridin-3-carboxilato de metilo (654 mg), trietilamina (4,79 mL) y diclorometano (20 mL) se añadió cloruro de titanio (IV) (566 µL) a 0 °C y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la

reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido marrón oscuro. A una mezcla del sólido obtenido, ácido acético (2 mL) y tetrahidrofurano (20 mL) se añadió cianoborohidruro de sodio (540 mg) y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar un sólido de color marrón pálido. A una mezcla del sólido obtenido, ácido trifluoroacético (1,00 mL) y etanol (10 mL) se añadió cianoborohidruro de sodio (251 mg) y la mezcla se agitó a temperatura ambiente durante 1 h. Además, se añadió cianoborohidruro de sodio (251 mg) y la mezcla se agitó a temperatura ambiente durante 30 min, luego a 50 °C durante 1 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (743 mg, 47%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 (d, J = 6,3 Hz, 3 H), 1,01 (d, J = 6,3 Hz, 3 H), 1,64 - 1,96 (m, 3 H), 2,48 (s, 3 H), 3,83 (s, 3 H), 5,25 - 5,40 (m, 2 H), 6,28 (d, J = 8,7 Hz, 1

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H), 7,24 - 7,39 (m, 2 H), 7,61 - 7,66 (m, 1 H), 7,71 - 7,76 (m, 1 H), 7,91 (dd, J = 8,7, 2,0 Hz, 1 H), 8,73 (d, J = 2,0 Hz, 1 H).

(2) ácido 6-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}piridin-3-carboxílico

Usando 6-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}piridin-3-carboxilato de metilo (743 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A23(4), se obtuvo el compuesto objeto del título (236 mg, 33%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 0,99 (m, 6 H), 1,58 - 1,78 (m, 2 H), 1,81 - 1,95 (m, 1 H), 2,44 (s, 3 H), 5,51 - 5,64 (m, 1 H), 6,53 (d, J = 8,7 Hz, 1 H), 7,24 - 7,38 (m, 2 H), 7,67 (d, J = 8,1 Hz, 1 H), 7,73 - 7,92 (m, 3 H), 8,50 (d, J = 2,4 Hz, 1 H), 12,29 (br s, 1 H).

(3) ácido 3-{[(6-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}piridin-3-il)carbonil]amino}propanoico

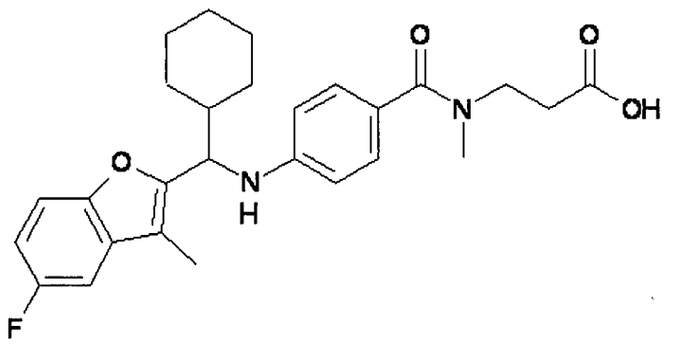
Usando ácido 6-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}piridin-3-carboxílico (115 mg) sintetizado con anterioridad y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (112 mg, 81%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 (d, J = 6,0 Hz, 3 H), 1,03 (d, J = 6,2 Hz, 3 H), 1,71 - 1,85 (m, 2 H), 1,95 - 2,11 (m, 1 H), 2,49 (s, 3 H), 2,57 - 2,67 (m, 2 H), 3,67 - 3,79 (m, 2 H), 4,86 - 4,98 (m, 1 H), 6,48 (d, J = 9,2 Hz, 1 H), 7,24 - 7,33 (m, 1 H), 7,33 - 7,41 (m, 1 H), 7,61 - 7,75 (m, 3 H), 8,10 - 8,20 (m, 2 H), 8,87 - 8,97 (m, 1 H).

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Ejemplo A37

Ácido 3-{[(4-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) 5-fluoro-N-metoxi-N,3-dimetil-1-benzofuran-2-carboxamida

A una mezcla de 1-(5-fluoro-2-hidroxifenil)etanona (10,0 g), 2-cloro-N-metoxi-N-metilacetamida (9,82 g), yoduro de sodio (19,5 g) y N,N-dimetilformamida (200 mL) se añadió carbonato de potasio (18,0 g) y la mezcla se agitó a 80 °C durante la noche. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido marrón. A una solución (200 mL) del sólido obtenido en N,N-dimetilformamida se añadió 1,8-diazabiciclo[5,4,0]undec-7-eno (9,71 mL) y la mezcla se agitó a 120 °C durante 4 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de

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sílice (acetato de etilo:hexano = 1:3, relación en volumen) para dar el compuesto objeto del título (4,37 g, 28%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,47 (s, 3 H), 3,38 (s, 3 H), 3,86 (s, 3 H), 6,98 - 7,16 (m, 1 H), 7,21 - 7,27 (m, 1 H), 7,37 - 7,43 (m, 1 H).

(2) ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metanol

A una solución (80 mL) de 5-fluoro-N-metoxi-N,3-dimetil-1-benzofuran-2-carboxamida (4,37 g) sintetizada con anterioridad en tetrahidrofurano se añadió gota a gota solución toluénica 1,5 M de hidruro de diisobutilaluminio (24,5 mL) a 0 °C y la mezcla se agitó durante 1 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:9, relación en volumen) para dar un sólido de color marrón pálido. A una solución (50 mL) del sólido obtenido en tetrahidrofurano se añadió gota a gota solución 1,0 M de bromuro de ciclohexilmagnesio en tetrahidrofurano (21,8 mL) a 0 °C y la mezcla se agitó durante 1 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 3:17, relación en volumen)

para dar el compuesto objeto del título (1,32 g, 27%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 - 1,43 (m, 6 H), 1,61 - 1,71 (m, 2 H), 1,75 - 1,98 (m, 3 H), 2,09 - 2,21 (m, 4 H), 4,51 (dd, J = 8,4, 6,0 Hz, 1 H), 6,92 - 7,00 (m, 1 H), 7,08 - 7,13 (m, 1 H), 7,30 - 7,36 (m, 1 H).

(3) 2-[cloro(ciclohexil)metil]-5-fluoro-3-metil-1-benzofurano

Usando ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metanol (1,01 g) sintetizado con anterioridad y de la misma manera que en el Ejemplo A11(3), se obtuvo el compuesto objeto del título (900 mg, 83%) en forma de un aceite de color amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,83 - 1,40 (m, 5 H), 1,40 - 1,50 (m, 1 H), 1,60 - 1,72 (m, 2 H), 1,77 - 1,88 (m, 1 H), 2,10 - 2,25 (m, 4 H), 2,28 - 2,38 (m, 1 H), 4,79 (d, J = 9,6 Hz, 1 H), 6,96 - 7,04 (m, 1 H), 7,09 - 7,14 (m, 1 H), 7,34 - 7,39 (m, 1 H).

(4) ácido 3-{[(4-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

Usando 2-[cloro(ciclohexil)metil]-5-fluoro-3-metil-1-benzofurano (400 mg) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (355 mg) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo A22(4), se obtuvo el compuesto objeto del título (303 mg, 46%) en forma de un sólido amarillo pálido.

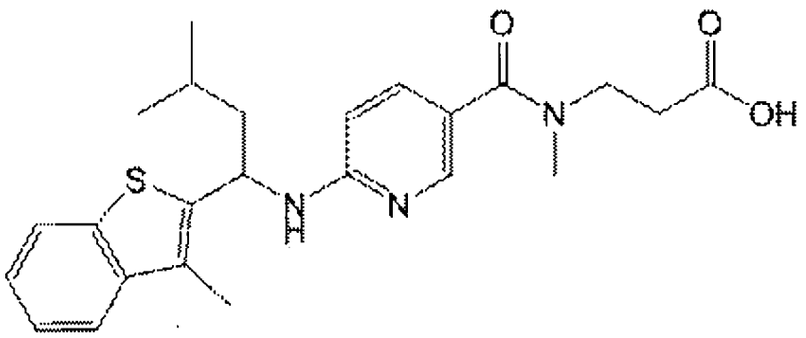
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,37 (m, 5 H), 1,45 - 1,56 (m, 1 H), 1,60 - 1,97 (m, 4 H), 2,03 - 2,14 (m, 1 H), 2,22 (s, 3 H), 2,64 (t, J = 6,5 Hz, 2 H), 3,02 (s, 3 H), 3,69

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(t, J = 6,5 Hz, 2 H), 4,36 (d, J = 7,9 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,88 - 6,97 (m, 1 H), 7,07 (dd, J = 8,5, 2,6 Hz, 1 H), 7,23 (d, J = 8,7 Hz, 2 H), 7,25 - 7,31 (m, 1 H).

Ejemplo A38

Ácido 3-{metil[(6-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}piridin-3-il)carbonil]amino}propanoico



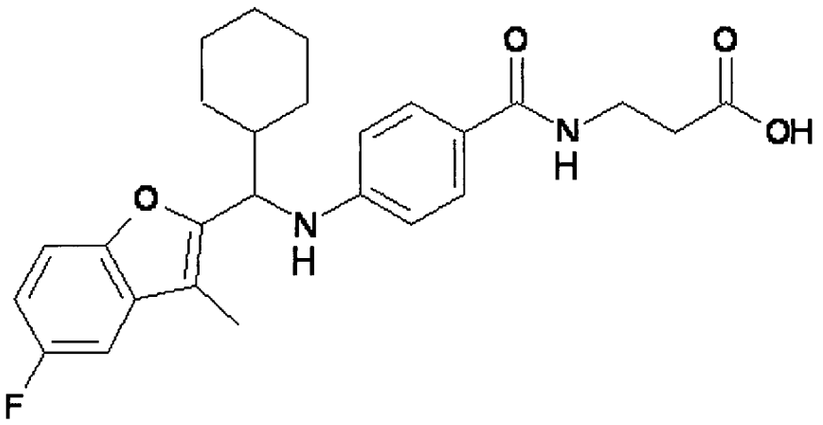
Usando ácido 6-{[3-metil-1-(3-metil-1-benzotiofen-2-il)butil]amino}piridin-3-carboxílico (121 mg) sintetizado en el Ejemplo A36(2) y 3-(metilamino)propanoato de etilo (67,2 mg) y de la misma manera que en el Ejemplo A1(4), se obtuvo el compuesto objeto del título (115 mg, 77%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 (d, J = 6,2 Hz, 3 H), 1,01 (d, J = 6,4 Hz, 3 H), 1,67 - 1,86 (m, 2 H), 1,93 - 2,08 (m, 1 H), 2,47 (s, 3 H), 2,62 - 2,71 (m, 2 H), 3,08 (s, 3 H), 3,67 - 3,84 (m, 2 H), 4,84 - 4,95 (m, 1 H), 6,35 (d, J = 8,9 Hz, 1 H), 7,24 - 7,31 (m, 1 H), 7,32 - 7,39 (m, 1 H), 7,51 - 7,59 (m, 1 H), 7,64 (d, J = 7,7 Hz, 1 H), 7,73 (d, J = 7,7 Hz, 1 H), 8,05 - 8,17 (m, 1 H).

Ejemplo A39

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Ácido 3-{[(4-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico

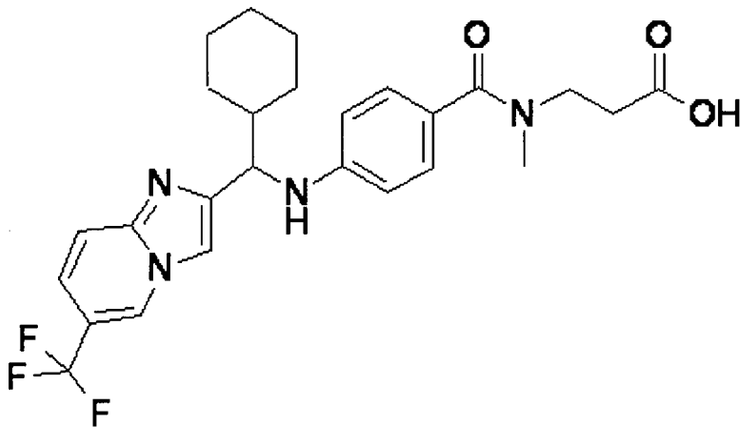



Usando 2-[cloro(ciclohexil)metil]-5-fluoro-3-metil-1-benzofurano (400 mg) sintetizado en el Ejemplo A37(3) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (336 mg) sintetizado en el Ejemplo 1(2) y de la misma manera que en el Ejemplo A22(4), se obtuvo el compuesto objeto del título (321 mg, 50%) en forma de un sólido de color marrón pálido.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 - 1,36 (m, 5 H), 1,43 - 1,56 (m, 1 H), 1,59 - 1,95 (m, 4 H), 2,00 - 2,12 (m, 1 H), 2,20 (s, 3 H), 2,59 (t, J = 5,7 Hz, 2 H), 3,55 - 3,67 (m, 2 H), 4,37 (d, J = 8,1 Hz, 1 H), 6,54 (d, J = 8,8 Hz, 2 H), 6,71 (t, J = 6,0 Hz, 1 H), 6,87 - 6,95 (m, 1 H), 7,05 (dd, J = 8,5, 2,4 Hz, 1 H), 7,21 - 7,30 (m, 1 H), 7,52 (d, J = 8,8 Hz, 2 H).

Ejemplo A40

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Ácido 3-[{[4-({ciclohexil[6-(trifluorometil)imidazo[1,2-a]piridin-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



(1) 6-(trifluorometil)imidazo[1,2-a]piridin-2-carbaldehído

A una solución de 5-(Trifluorometil)piridin-2-amina (12,9 g) se disolvió en dimetoxietano (150 mL) se añadió 1,1,3-tricloroacetona (12,7 mL) a temperatura ambiente y la mezcla se agitó durante la noche. El sólido precipitado se recogió y se suspendió en etanol (50 mL) y la mezcla se calentó a reflujo durante 3 h. Después de enfriar hasta temperatura ambiente, el solvente se evaporó a presión reducida, el carbonato ácido de sodio acuoso saturado se añadió al residuo y la mezcla se extrajo con acetato de etilo-tetrahidrofurano (1:1, relación en volumen). El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar

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2-(diclorometil)-6-(trifluorometil)imidazo[1,2-a]piridina (10,3 g) en forma de un sólido blanco. El sólido obtenido se suspendió en un solvente mixto de agua (100 mL) y tetrahidrofurano (20 mL) y carbonato de calcio (8,0 g) se añadió a la mezcla a temperatura ambiente y la mezcla se agitó a 100 °C durante 1 h. La mezcla se dejó enfriar hasta temperatura ambiente, el material insoluble se filtró y el filtrado se extrajo con acetato de etilo. El extracto se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido blanco. El residuo se lavó con éter diisopropílico para dar el compuesto objeto del título (7,3 g, 43%) en forma de cristales blancos.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 7,43 (d, J = 9,8 Hz, 1 H), 7,82 (d, J = 9,8 Hz, 1H), 8,26 (s, 1 H), 8,58 (s, 1 H), 10,19 (s, 1 H).

(2) ciclohexil[6-(trifluorometil)imidazo[1,2-a]piridin-2-il]metanol

A una solución de 6-(trifluorometil)imidazo[1,2-a]piridin-2-carbaldehído (2,1 g) sintetizado con anterioridad en tetrahidrofurano (40 mL) se añadió gota a gota bromuro de ciclohexilmagnesio (solución 1 M de tetrahidrofurano, 15 mL) a 0 °C. Después de agitar a 0 °C durante 1 h, se añadió solución acuosa de cloruro de amonio. La mezcla se extrajo con acetato de etilo y el solvente se evaporó a presión reducida. El precipitado se lavó con etanol-éter diisopropílico para dar el compuesto objeto del título (0,9 g, 30%) en forma de un sólido incoloro.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,01 - 1,96 (m, 11 H), 2,43 (d, J = 6,1 Hz, 1 H), 4,66 (t, J = 5,9 Hz, 1 H), 7,31 (d, J = 9,8 Hz, 1 H), 7,59 (s, 1 H), 7,66 (d, J = 9,8 Hz, 1 H), 8,46 (s, 1 H).

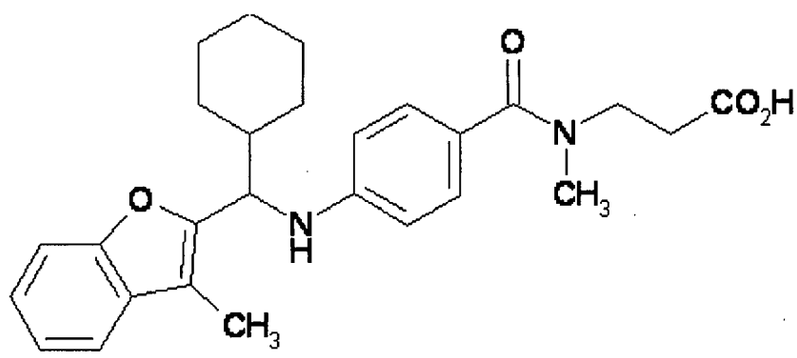
(3) ácido 3-[{[4-({ciclohexil[6-(trifluorometil)imidazo[1,2-a]piridin-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

Usando ciclohexil[6-(trifluorometil)imidazo[1,2-a]piridin-2-il]metanol (1,1 g) sintetizado con anterioridad y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,94 g) sintetizado en el Ejemplo 2(2) y de la misma manera que en el Ejemplo 4, se obtuvo el compuesto objeto del título (3,0 mg, 2%) en forma de un aceite.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 - 2,16 (m, 11 H), 2,50 - 2,75 (m, 2 H), 3,06 (s, 3 H), 3,10 - 3,25 (br s, 1 H), 3,61 - 3,82 (m, 2 H), 4,43 (d, J = 6,0 Hz, 1 H), 6,54 (d, J = 9,0 Hz, 2 H), 7,16 (d, J = 9,0 Hz, 2 H), 7,45 (d, J = 9,0 Hz, 1 H), 7,63 (s, 1 H), 7,84 (d, J = 9,0 Hz, 1 H), 8,53 (s, 1 H).

Ejemplo A41

Ácido 3-{[(4-{[ciclohexil(3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico



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El 3-{[(4-{[ciclohexil(3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (9,85 g) sintetizado en el Ejemplo A16 se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm IDx500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (500/500), velocidad de flujo: 60 mL/min, temperatura de la columna: temperatura ambiente). La fracción que contenía una forma ópticamente activa con un tiempo de retención más corto en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (4,85 g, 99,9% ee). A una mezcla de la forma amorfa obtenida, etanol (20 mL) y tetrahidrofurano (20 mL) se añadió solución acuosa 1 N de hidróxido de litio (22 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (20 mL) y ácido clorhídrico 1 N (20 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (4,41 g, 97%, 99,9% ee) en forma de un sólido blanco. El sólido blanco obtenido (50 mg) se cristalizó en etanol/agua para dar cristales con contenido de etanol (41 mg). Los cristales con contenido de etanol (35 mg) se recristalizaron en éter dietílico para dar cristal incoloro (18 mg) libre de solvent.

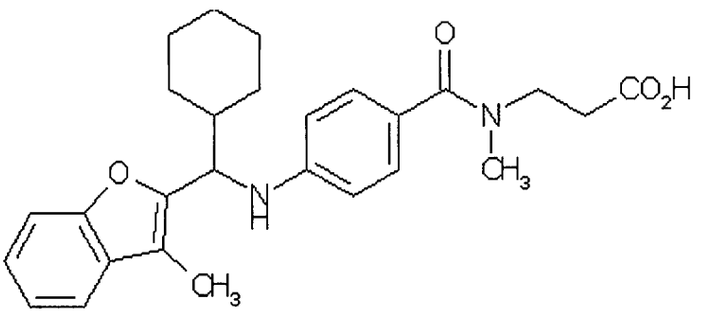
$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,97 - 1,28 (m, 5 H) 1,30 - 1,39 (m, 1 H) 1,52 - 1,81 (m, 3 H) 1,81 - 2,00 (m, 1 H) 2,03

1237

- 2,18 (m, 1 H) 2,26 (s, 3 H) 2,40 - 2,49 (m, 2 H) 2,88 (s, 3 H) 3,50 (t, J = 7,38 Hz, 2 H) 4,41 (t, J = 8,33 Hz, 1 H) 6,48 (d, J = 7,95 Hz, 1 H) 6,60 (d, J = 8,71 Hz, 2 H) 7,09 (d, J = 8,33 Hz, 2 H) 7,14 - 7,29 (m, 2 H) 7,36 - 7,55 (m, 2 H) 12,27 (brs, 1 H).

Ejemplo A42

Ácido 3-{[(4-{[ciclohexil(3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




El 3-{[(4-{[ciclohexil(3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (9,85 g) sintetizado en el Ejemplo A16 se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm IDx500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (500/500), velocidad de flujo: 60 mL/min, temperatura de la columna: temperatura ambiente). La fracción que contenía una forma ópticamente activa con un tiempo de retención más largo en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (4,81 g, 99,9% ee). A una mezcla de la forma amorfa obtenida,

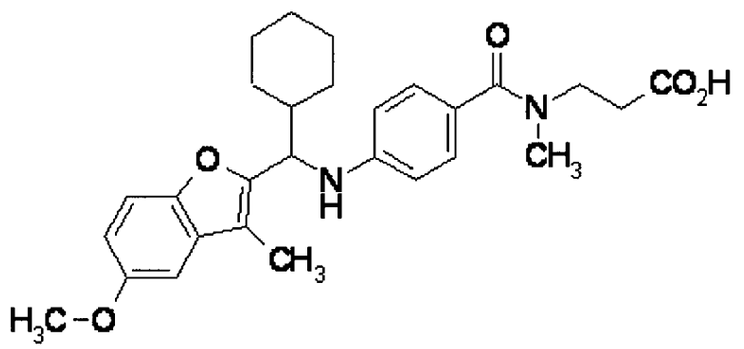
1238

etanol (20 mL) y tetrahidrofurano (20 mL) se añadió solución acuosa 1 N de hidróxido de litio (22 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (20 mL) y ácido clorhídrico 1 N (20 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (4,43 g, 98%, 99,9% ee) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,97 - 1,28 (m, 5 H) 1,30 - 1,39 (m, 1 H) 1,52 - 1,81 (m, 3 H) 1,81 - 2,00 (m, 1 H) 2,03 - 2,18 (m, 1 H) 2,26 (s, 3 H) 2,40 - 2,49 (m, 2 H) 2,88 (s, 3 H) 3,50 (t, J = 7,38 Hz, 2 H) 4,41 (t, J = 8,33 Hz, 1 H) 6,48 (d, J = 7,95 Hz, 1 H) 6,60 (d, J = 8,71 Hz, 2 H) 7,09 (d, J = 8,33 Hz, 2 H) 7,14 - 7,29 (m, 2 H) 7,36 - 7,55 (m, 2 H) 12,27 (brs, 1 H).

Ejemplo A43

Ácido 3-{[(4-{[ciclohexil(5-metoxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) ácido 4-{[ciclohexil(5-metoxi-3-metil-1-benzofuran-2-il)metil]amino}benzoico

1239

A una mezcla de 2-[cloro(ciclohexil)metil]-5-metoxi-3-metil-1-benzofurano (748 mg) sintetizado en el Ejemplo A27(4), 4-aminobenzoato de metilo (385 mg), yoduro de sodio (764 mg) y N,N-dimetilformamida (15 mL) se añadió carbonato de sodio (541 mg) y la mezcla se agitó a 80 °C durante la noche. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (25% de acetato de etilo/hexano) para dar un aceite amarillo. A una mezcla del aceite obtenido, tetrahidrofurano (20 mL) y etanol (20 mL) se añadió solución acuosa 1 N de hidróxido de sodio (20 mL) y la mezcla se agitó con calentamiento a reflujo durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (40 mL) y ácido clorhídrico 1 N (20 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (745 mg, 74%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,37 (m, 5 H), 1,47 - 1,58 (m, 1 H), 1,61 - 1,98 (m, 4 H), 2,02 - 2,12 (m, 1 H), 2,24 (s, 3 H), 3,83 (s, 3 H), 4,42 (d, J = 7,9 Hz, 1 H), 6,57 (d, J = 8,9 Hz, 2 H), 6,83 (dd, J = 8,8, 2,5 Hz, 1 H), 6,88 (d, J = 2,5 Hz, 1 H), 7,26 (d, J = 8,8 Hz, 1 H), 7,85 (d, J = 8,9 Hz, 2 H).

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(2) 3-{[(4-{[ciclohexil(5-metoxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclohexil(5-metoxi-3-metil-1-benzofuran-2-il)metil]amino}benzoico (745 mg) sintetizado con anterioridad, 3-(metilamino)propanoato de etilo (298 mg), monohidrato de 1-hidroxibenzotriazol (348 mg), trietilamina (633 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (435 mg) y la mezcla se agitó a temperatura ambiente durante la noche, luego a 50 °C durante 3 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (55% de acetato de etilo/hexano) para dar el compuesto objeto del título (801 mg, 84%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,35 (m, 8 H), 1,47 - 1,60 (m, 1 H), 1,60 - 1,97 (m, 4 H), 2,02 - 2,14 (m, 1 H), 2,22 (s, 3 H), 2,61 (t, J = 7,0 Hz, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,0 Hz, 2 H), 3,84 (s, 3 H), 4,07 - 4,17 (m, 2 H), 4,30 - 4,40 (m, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,82 (dd, J = 8,9, 2,6 Hz, 1 H), 6,88 (d, J = 2,6 Hz, 1 H), 7,18 - 7,30 (m, 3 H).

(3) ácido 3-{[(4-{[ciclohexil(5-metoxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

1241

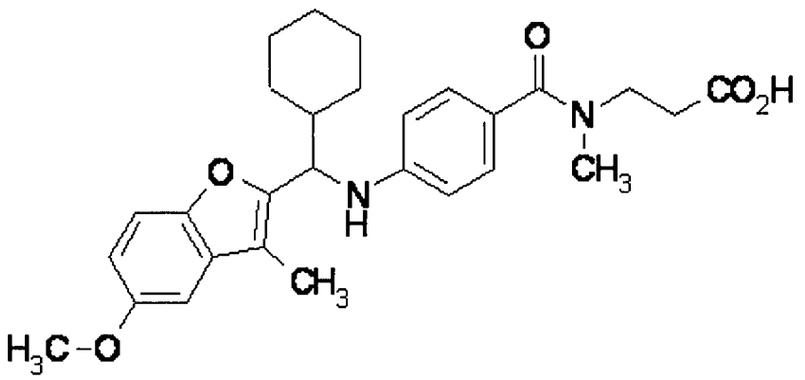
El 3-{[(4-{[ciclohexil(5-metoxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (795 mg) sintetizado con anterioridad se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm IDx500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (400/600), velocidad de flujo: 60 mL/min, temperatura de la columna: 30 °C). La fracción que contenía una forma ópticamente activa con un tiempo de retención más corto en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (413 mg, 99,9% ee). A una mezcla de la forma amorfa obtenida, etanol (5 mL) y tetrahidrofurano (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (355 mg, 47%, 99,9% ee) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,37 (m, 5 H), 1,47 - 1,57 (m, 1 H), 1,60 - 1,96 (m, 4 H), 2,03 - 2,13 (m, 1 H), 2,23 (s, 3 H), 2,65 (t, J = 6,4 Hz, 2 H), 3,02 (s, 3 H), 3,69 (t, J = 6,4 Hz, 2 H), 3,83 (s, 3 H), 4,36 (d, J = 8,0 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,82 (dd, J = 8,9, 2,4 Hz, 1 H), 6,88 (d, J = 2,4 Hz, 1 H), 7,19 - 7,29 (m, 3 H).

Ejemplo A44

1242

Ácido 3-{[(4-{[ciclohexil(5-metoxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




El 3-{[(4-{[ciclohexil(5-metoxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (795 mg) sintetizado en el Ejemplo A43(2) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm IDx500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (400/600), velocidad de flujo: 60 mL/min, temperatura de la columna: 30 °C). La fracción que contenía una forma ópticamente activa con un tiempo de retención más largo en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (418 mg, 99,9% ee). A una mezcla de la forma amorfa obtenida, etanol (5 mL) y tetrahidrofurano (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 1,5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado

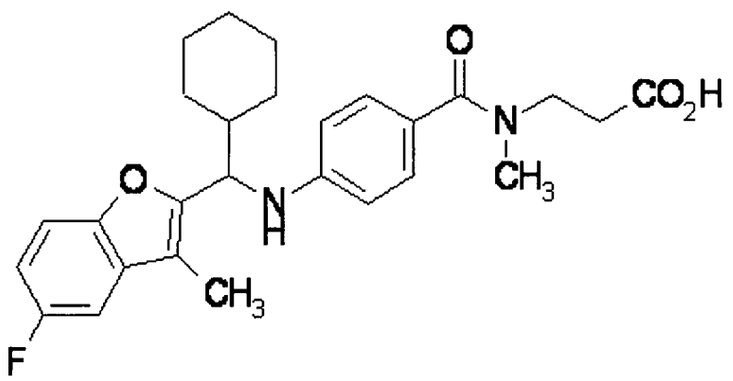
1243

resultante se recogió por filtración para dar el compuesto objeto del título (354 mg, 47%, 99,9% ee) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,37 (m, 5 H), 1,47 - 1,57 (m, 1 H), 1,60 - 1,96 (m, 4 H), 2,03 - 2,13 (m, 1 H), 2,23 (s, 3 H), 2,65 (t, J = 6,4 Hz, 2 H), 3,02 (s, 3 H), 3,69 (t, J = 6,4 Hz, 2 H), 3,83 (s, 3 H), 4,36 (d, J = 8,0 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,82 (dd, J = 8,9, 2,4 Hz, 1 H), 6,88 (d, J = 2,4 Hz, 1 H), 7,19 - 7,29 (m, 3 H).

Ejemplo A45

Ácido 3-{[(4-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) Ácido 4-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}benzoico

A una mezcla de 2-[cloro(ciclohexil)metil]-5-fluoro-3-metil-1-benzofurano (1,44 g) sintetizado en el Ejemplo A37(3), 4-aminobenzoato de metilo (776 mg), yoduro de sodio (1,54 g) y N,N-dimetilformamida (30 mL) se añadió carbonato de sodio (1,09 g) y la mezcla se agitó a 80 °C durante la

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noche. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (20% de acetato de etilo/hexano) para dar un sólido amarillo. A una mezcla del sólido obtenido, tetrahidrofurano (20 mL) y etanol (20 mL) se añadió solución acuosa 1 N de hidróxido de sodio (20 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (40 mL) y ácido clorhídrico 1 N (20 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (1,06 g, 54%) en forma de un sólido amarillo.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,37 (m, 5 H), 1,46 - 1,58 (m, 1 H), 1,60 - 1,99 (m, 4 H), 2,02 - 2,13 (m, 1 H), 2,23 (s, 3 H), 4,43 (d, J = 8,0 Hz, 1 H), 4,51 - 4,73 (m, 1 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,87 - 6,98 (m, 1 H), 7,04 - 7,11 (m, 1 H), 7,24 - 7,32 (m, 1 H), 7,85 (d, J = 8,7 Hz, 2 H).

(2) 3-{[(4-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}benzoico (1,06 g) sintetizado con anterioridad, 3-(metilamino)propanoato de etilo (438 mg), monohidrato de 1-hidroxibenzotriazol (512 mg), trietilamina (930 µL) y N,N-dimetilformamida (20 mL) se añadió clorhidrato

1245

de 1-etil-3-(3-dimetilaminopropil)carbodiimida (640 mg) y la mezcla se agitó a temperatura ambiente durante 1,5 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (55% de acetato de etilo/hexano) para dar el compuesto objeto del título (564 mg, 41%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,37 (m, 8 H), 1,46 - 1,56 (m, 1 H), 1,61 - 1,98 (m, 4 H), 2,03 - 2,14 (m, 1 H), 2,22 (s, 3 H), 2,61 (t, J = 7,0 Hz, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,0 Hz, 2 H), 4,06 - 4,17 (m, 2 H), 4,28 - 4,41 (m, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,88 - 6,97 (m, 1 H), 7,04 - 7,09 (m, 1 H), 7,22 (d, J = 8,7 Hz, 2 H), 7,25 - 7,31 (m, 1 H).

(3) ácido 3-{[(4-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

El 3-{[(4-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (564 mg) sintetizado con anterioridad se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm ID×500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (400/600), velocidad de flujo: 60 mL/min, temperatura de la columna: 30 °C). La fracción que contenía una forma ópticamente activa con un tiempo de retención más corto en las condiciones antes

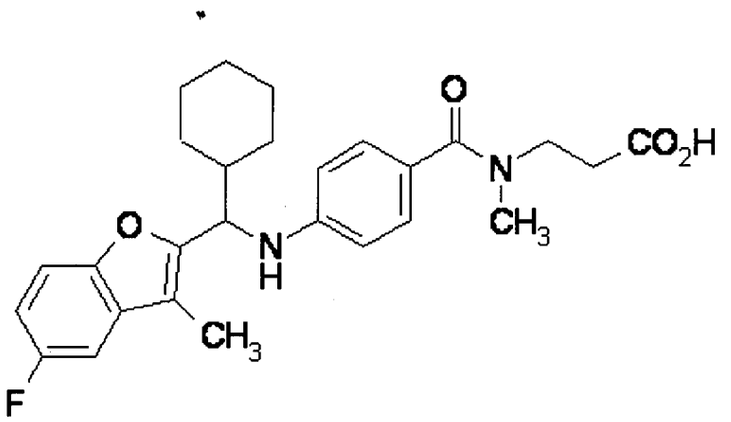
1246

mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (274 mg, 99,9% ee). A una mezcla de la forma amorfa obtenida, etanol (5 mL) y tetrahidrofurano (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 1,5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (249 mg, 47%, 99,9% ee) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,37 (m, 5 H), 1,45 - 1,56 (m, 1 H), 1,60 - 1,97 (m, 4 H), 2,03 - 2,14 (m, 1 H), 2,22 (s, 3 H), 2,64 (t, J = 6,5 Hz, 2 H), 3,02 (s, 3 H), 3,69 (t, J = 6,5 Hz, 2 H), 4,36 (d, J = 7,9 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,88 - 6,97 (m, 1 H), 7,07 (dd, J = 8,5, 2,6 Hz, 1 H), 7,23 (d, J = 8,7 Hz, 2 H), 7,25 - 7,31 (m, 1 H).

Ejemplo A46

Ácido 3-{[(4-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico



1247

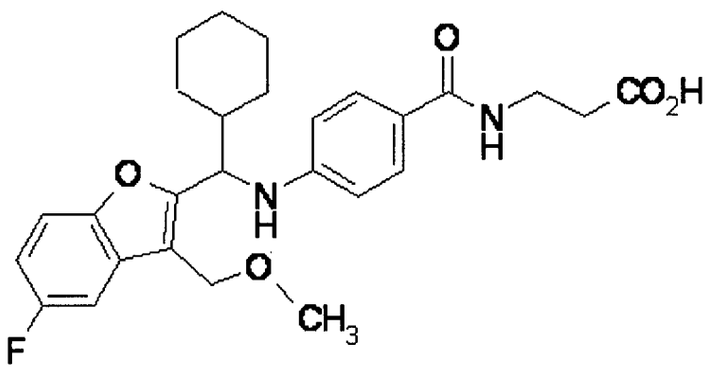
El 3-{[(4-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (564 mg) sintetizado en el Ejemplo A45(2) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm IDx500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (400/600), velocidad de flujo: 60 mL/min, temperatura de la columna: 30 °C). La fracción que contenía una forma ópticamente activa con un tiempo de retención más largo en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (273 mg, 99,9% ee). A una mezcla de la forma amorfa obtenida, etanol (5 mL) y tetrahidrofurano (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 1,5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (248 mg, 47%, 99,9% ee) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,37 (m, 5 H), 1,45 - 1,56 (m, 1 H), 1,60 - 1,97 (m, 4 H), 2,03 - 2,14 (m, 1 H), 2,22 (s, 3 H), 2,64 (t, J = 6,5 Hz, 2 H), 3,02 (s, 3 H), 3,69 (t, J = 6,5 Hz, 2 H), 4,36 (d, J = 7,9 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,88 - 6,97 (m, 1 H), 7,07 (dd, J = 8,5, 2,6 Hz, 1 H), 7,23 (d, J = 8,7 Hz, 2 H), 7,25 - 7,31 (m, 1 H).

Ejemplo A47

1248

Ácido 3-({[4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metil}amino)fenil]carbonil}amino)propanoico



(1) 5-fluoro-3-metil-1-benzofuran-2-carboxilato de metilo

A una mezcla de 1-(5-fluoro-2-hidroxifenil)etanona (100 g), bromoacetato de metilo (67,6 mL) y N,N-dimetilformamida (500 mL) se añadió carbonato de potasio (135 g) y la mezcla se agitó a 50 °C durante 2 h. El material insoluble se filtró, se añadió 1,8-diazabiciclo[5,4,0]undec-7-eno (97,1 mL) y la mezcla se agitó a 120 °C durante 30 min. Se añadió ácido clorhídrico 1 N a la mezcla de reacción a 0 °C y el precipitado resultante se recogió por filtración para dar el compuesto objeto del título (77,9 g, 58%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,56 (s, 3 H), 3,99 (s, 3 H), 7,14 - 7,22 (m, 1 H), 7,24 - 7,30 (m, 1 H), 7,45 - 7,51 (m, 1 H).

(2) 3-(bromometil)-5-fluoro-1-benzofuran-2-carboxilato de metilo

A una solución (150 mL) de 5-fluoro-3-metil-1-benzofuran-2-carboxilato de metilo (15,4 g) sintetizado con anterioridad en acetonitrilo se añadieron N-bromosuccinimida (19,8 g) y 2,2'-azobis(isobutironitrilo) (1,21 g) y la mezcla se agitó bajo una atmósfera de argón a 50 °C durante 2,5 días. La mezcla de reacción se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (20 - 30% de acetato de etilo/hexano) para dar un sólido blanco. El sólido obtenido se lavó con hexano para dar el compuesto objeto del título (15,1 g, 71%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 4,02 (s, 3 H), 4,96 (s, 2 H), 7,18 - 7,27 (m, 1 H), 7,41 - 7,47 (m, 1 H), 7,49 - 7,55 (m, 1 H).

(3) 5-fluoro-3-(metoximetil)-1-benzofuran-2-carboxilato de metilo

A una solución (50 mL) de 3-(bromometil)-5-fluoro-1-benzofuran-2-carboxilato de metilo (5,87 g) sintetizada con anterioridad en metanol se añadió solución al 28% (8,33 mL) de metóxido de sodio en metanol y la mezcla se agitó con calentamiento a reflujo durante 3 h. Se añadió ácido clorhídrico 1 N a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (50% de acetato de etilo/hexano) para dar el compuesto objeto del título (3,04 g, 63%) en forma de un sólido blanco.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,44 (s, 3 H), 3,99 (s, 3 H), 4,99 (s, 2 H), 7,18 (td, J = 9,1, 2,7 Hz, 1 H), 7,46 - 7,52 (m, 1 H), 7,53 - 7,58 (m, 1 H).

(4) 5-fluoro-3-(metoximetil)-1-benzofuran-2-carbaldehído

A una mezcla de 5-fluoro-3-(metoximetil)-1-benzofuran-2-carboxilato de metilo (5,01 g) sintetizado con anterioridad, cloruro de calcio (4,66 g), etanol (50 mL) y tetrahidrofurano (50 mL) se añadió a 0 °C borohidruro de sodio (3,18 g) y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción, el solvente orgánico se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite incoloro. A una mezcla del aceite obtenido, se añadió N-óxido de 4-metilmorfolina (3,69 g) y acetonitrilo (50 mL) perrutenato de tetrapropilamonio (738 mg) a 0 °C y la mezcla se agitó durante 1,5 h y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 20% de acetato de etilo/hexano) para dar el compuesto objeto del título (2,33 g, 53%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,49 (s, 3 H), 4,94 (s, 2 H), 7,21 - 7,29 (m, 1 H), 7,47 - 7,54 (m, 2 H), 10,08 (s, 1 H).

(5) ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metanona

A una solución (20 mL) de 5-fluoro-3-(metoximetil)-1-benzofuran-2-carbaldehído (1,07 g) sintetizada con

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anterioridad en tetrahidrofurano se añadió una solución 1,0 M (7,71 mL) de bromuro de ciclohexilmagnesio en tetrahidrofurano a 0 °C y la mezcla se agitó durante 1 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción, el tetrahidrofurano se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (10 - 50% de acetato de etilo/hexano) para dar un aceite de color amarillo pálido. A una mezcla del aceite obtenido, N-óxido de 4-metilmorfolina (841 mg) y acetonitrilo (20 mL) se añadió perrutenato de tetrapropilamonio (126 mg) y la mezcla se agitó a temperatura ambiente durante 1,5 h y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 20% de acetato de etilo/hexano) para dar el compuesto objeto del título (857 mg, 57%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,15 - 1,55 (m, 5 H), 1,69 - 1,80 (m, 1 H), 1,80 - 2,02 (m, 4 H), 3,25 - 3,39 (m, 1 H), 3,44 (s, 3 H), 5,00 (s, 2 H), 7,15 - 7,23 (m, 1 H), 7,43 - 7,49 (m, 1 H), 7,57 - 7,62 (m, 1 H).

(6) 4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metil}amino)benzoato de metilo

A una mezcla de ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metanona (857 mg) sintetizada con anterioridad, 4-aminobenzoato de metilo (491 mg),

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trietilamina (3,29 mL) y cloruro de metileno (10 mL) se añadió cloruro de titanio (IV) (388 µL) y la mezcla se agitó bajo una atmósfera de argón a temperatura ambiente durante la noche. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción, el cloruro de metileno se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (20 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (847 µL) y cianoborohidruro de sodio (371 mg) y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 40% de acetato de etilo/hexano) para dar el compuesto objeto del título (454 mg, 36%) en forma de un aceite de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 - 1,36 (m, 5 H), 1,43 - 1,54 (m, 1 H), 1,60 - 1,99 (m, 4 H), 2,00 - 2,11 (m, 1 H), 3,37 (s, 3 H), 3,81 (s, 3 H), 4,48 - 4,64 (m, 4 H), 6,60 (d, J = 8,8 Hz, 2 H), 6,90 - 6,99 (m, 1 H), 7,17 - 7,23 (m, 1 H), 7,28 - 7,34 (m, 1 H), 7,79 (d, J = 8,8 Hz, 2 H).

(7) Ácido 4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metil}amino)benzoico

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A una mezcla de 4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metil}amino)benzoato de metilo (454 mg) sintetizado con anterioridad, tetrahidrofurano (10 mL) y etanol (10 mL) se añadió solución acuosa 1 N de hidróxido de sodio (10,0 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (20 mL) y ácido clorhídrico 1 N (10,0 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (423 mg, 96%) en forma de un sólido blanco.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 1,36 (m, 5 H), 1,40 - 1,55 (m, 1 H), 1,60 - 1,99 (m, 4 H), 1,99 - 2,13 (m, 1 H), 3,38 (s, 3 H), 4,49 - 4,77 (m, 4 H), 6,61 (d, J = 8,8 Hz, 2 H), 6,90 - 6,99 (m, 1 H), 7,17 - 7,23 (m, 1 H), 7,28 - 7,35 (m, 1 H), 7,84 (d, J = 8,8 Hz, 2 H).

(8) 3-({[4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metil}amino)fenil]carbonil}amino)propanoato de etilo

A una mezcla de ácido 4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metil}amino)benzoico (200 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (112 mg), monohidrato de 1-hidroxibenzotriazol (112 mg), trietilamina (203 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (140 mg) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de

etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (207 mg, 83%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,36 (m, 8 H), 1,42 - 1,54 (m, 1 H), 1,60 - 1,97 (m, 4 H), 2,01 - 2,13 (m, 1 H), 2,58 (t, J = 5,8 Hz, 2 H), 3,37 (s, 3 H), 3,61 - 3,70 (m, 2 H), 4,13 (q, J = 7,1 Hz, 2 H), 4,46 - 4,62 (m, 4 H), 6,56 - 6,65 (m, 3 H), 6,90 - 6,99 (m, 1 H), 7,17 - 7,23 (m, 1 H), 7,27 - 7,33 (m, 1 H), 7,54 (d, J = 8,8 Hz, 2 H).

(9) ácido 3-({[4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metil}amino)fenil]carbonil}amino)propanoico

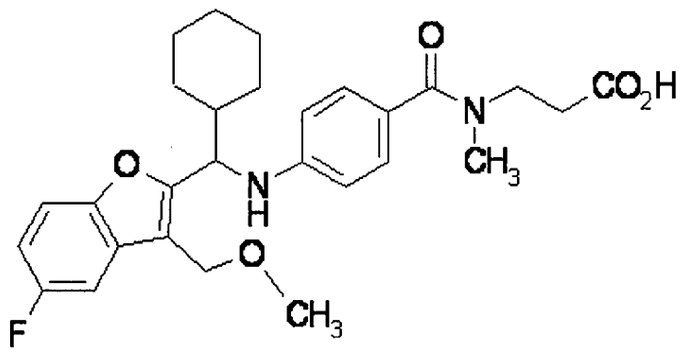
A una mezcla de 3-({[4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metil}amino)fenil]carbonil}amino)propanoato de etilo (207 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (186 mg, 95%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,35 (m, 5 H), 1,41 - 1,53 (m, 1 H), 1,60 - 1,97 (m, 4 H), 2,00 - 2,11 (m, 1 H),

2,63 (t, J = 5,7 Hz, 2 H), 3,37 (s, 3 H), 3,59 - 3,68 (m, 2 H), 4,50 (d, J = 8,1 Hz, 1 H), 4,54 (d, J = 12,2 Hz, 1 H), 4,59 (d, J = 12,2 Hz, 1 H), 6,55 - 6,66 (m, 3 H), 6,90 - 6,99 (m, 1 H), 7,16 - 7,23 (m, 1 H), 7,27 - 7,34 (m, 1 H), 7,53 (d, J = 8,9 Hz, 2 H).

Ejemplo A48

Ácido 3-[{[4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



(1) 3-[{[4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

A una mezcla de ácido 4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metil}amino)benzoico (200 mg) sintetizado en el Ejemplo A47(7), 3-(metilamino)propanoato de etilo (95,6 mg), monohidrato de 1-hidroxibenzotriazol (112 mg), trietilamina (203 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-

dimetilaminopropil)carbodiimida (140 mg) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (197 mg, 77%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 1,36 (m, 8 H), 1,42 - 1,53 (m, 1 H), 1,59 - 1,97 (m, 4 H), 2,02 - 2,13 (m, 1 H), 2,61 (t, J = 7,0 Hz, 2 H), 3,00 (s, 3 H), 3,36 (s, 3 H), 3,70 (t, J = 7,0 Hz, 2 H), 4,11 (q, J = 7,1 Hz, 2 H), 4,35 - 4,51 (m, 2 H), 4,54 (d, J = 12,3 Hz, 1 H), 4,59 (d, J = 12,3 Hz, 1 H), 6,59 (d, J = 8,5 Hz, 2 H), 6,90 - 6,99 (m, 1 H), 7,17 - 7,24 (m, 3 H), 7,28 - 7,34 (m, 1 H).

(2) ácido 3-[{[4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-
il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una mezcla de 3-[{[4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-
il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (197 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 7 h y se concentró a presión

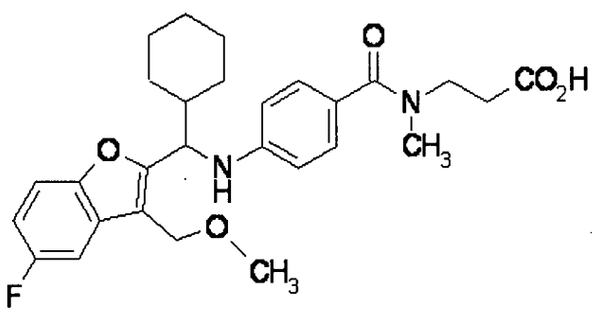
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reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (161 mg, 87%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,36 (m, 5 H), 1,41 - 1,53 (m, 1 H), 1,59 - 1,97 (m, 4 H), 2,01 - 2,13 (m, 1 H), 2,54 - 2,70 (m, 2 H), 3,01 (s, 3 H), 3,37 (s, 3 H), 3,68 (t, J = 6,6 Hz, 2 H), 4,47 (d, J = 7,9 Hz, 1 H), 4,55 (d, J = 12,2 Hz, 1 H), 4,60 (d, J = 12,2 Hz, 1 H), 6,59 (d, J = 8,5 Hz, 2 H), 6,89 - 7,00 (m, 1 H), 7,17 - 7,25 (m, 3 H), 7,28 - 7,35 (m, 1 H).

Ejemplo A49

Ácido 3-[{[4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico




3-[{[4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (1,20 g) sintetizado en el Ejemplo A48(1) se fraccionó

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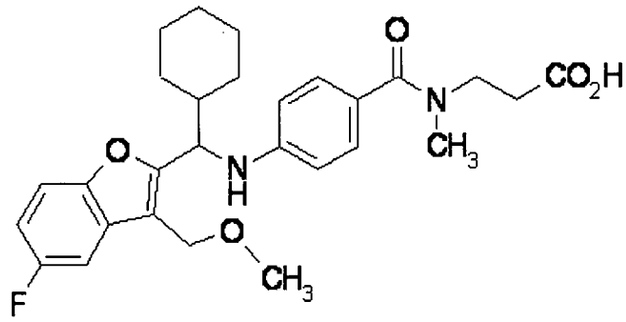
por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm ID×500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (200/800), velocidad de flujo: 60 mL/min, temperatura de la columna: 30 °C). La fracción que contenía una forma ópticamente activa con un tiempo de retención más corto en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (470 mg, 99,9% ee). A una mezcla de la forma amorfa obtenida, etanol (5 mL) y tetrahidrofurano (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (433 mg, 38%, 99,9% ee) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,36 (m, 5 H), 1,41 - 1,53 (m, 1 H), 1,59 - 1,97 (m, 4 H), 2,01 - 2,13 (m, 1 H), 2,54 - 2,70 (m, 2 H), 3,01 (s, 3 H), 3,37 (s, 3 H), 3,68 (t, J = 6,6 Hz, 2 H), 4,47 (d, J = 7,9 Hz, 1 H), 4,55 (d, J = 12,2 Hz, 1 H), 4,60 (d, J = 12,2 Hz, 1 H), 6,59 (d, J = 8,5 Hz, 2 H), 6,89 - 7,00 (m, 1 H), 7,17 - 7,25 (m, 3 H), 7,28 - 7,35 (m, 1 H).

Ejemplo A50

Ácido 3-[{[4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

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El 3-[{[4-({ciclohexil[5-fluoro-3-(metoximetil)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (1,20 g) sintetizado en el Ejemplo A48(1) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm ID×500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (200/800), velocidad de flujo: 60 mL/min, temperatura de la columna: 30 °C). La fracción que contenía una forma ópticamente activa con un tiempo de retención más largo en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (465 mg, 99,9% ee). A una mezcla de la forma amorfa obtenida, etanol (5 mL) y tetrahidrofurano (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto

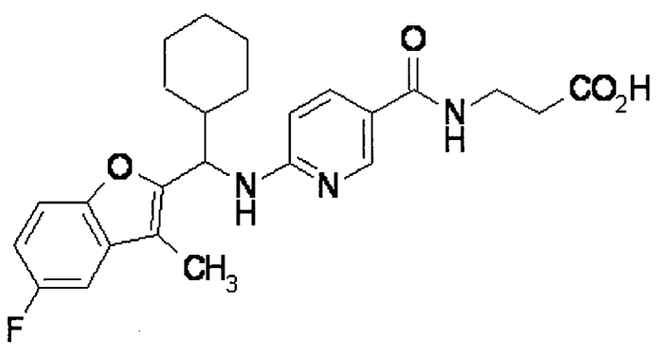
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objeto del título (415 mg, 37%, 99,9% ee) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,36 (m, 5 H), 1,41 - 1,53 (m, 1 H), 1,59 - 1,97 (m, 4 H), 2,01 - 2,13 (m, 1 H), 2,54 - 2,70 (m, 2 H), 3,01 (s, 3 H), 3,37 (s, 3 H), 3,68 (t, J = 6,6 Hz, 2 H), 4,47 (d, J = 7,9 Hz, 1 H), 4,55 (d, J = 12,2 Hz, 1 H), 4,60 (d, J = 12,2 Hz, 1 H), 6,59 (d, J = 8,5 Hz, 2 H), 6,89 - 7,00 (m, 1 H), 7,17 - 7,25 (m, 3 H), 7,28 - 7,35 (m, 1 H).

Ejemplo A51

Ácido 3-{[(6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil]amino}propanoico




(1) 2-bromo-1-ciclohexiletanona

A una solución (50 mL) de 1-ciclohexiletanona (25,0 g) en metanol se añadió bromo (10,1 mL) a 0 °C y la mezcla se agitó a temperatura ambiente durante 30 min. Se añadió solución acuosa saturada de sulfito de sodio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se

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purificó por cromatografía en columna de gel de sílice (0 - 10% de acetato de etilo/hexano) para dar el compuesto objeto del título (25,8 g, 63%) en forma de un aceite incoloro. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,10 - 1,50 (m, 5 H), 1,62 - 1,73 (m, 1 H), 1,75 - 1,94 (m, 4 H), 2,64 - 2,79 (m, 1 H), 3,97 (s, 2 H).

(2) ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metanona

A una mezcla de 5'-fluoro-2'-hidroxiacetofenona (5,00 g), 2-bromo-1-ciclohexiletanona (7,98 g) sintetizada con anterioridad y N,N-dimetilformamida (50 mL) se añadió carbonato de potasio (13,4 g) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 20% de acetato de etilo/hexano) para dar el compuesto objeto del título (5,38 g, 64%) en forma de un sólido amarillo pálido. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,19 - 1,57 (m, 5 H), 1,70 - 2,01 (m, 5 H), 2,56 (s, 3 H), 3,25 - 3,36 (m, 1 H), 7,15 - 7,23 (m, 1 H), 7,24 - 7,30 (m, 1 H), 7,42 - 7,48 (m, 1 H).

(3) 6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-carboxilato de metilo

A una mezcla de ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metanona (3,00 g) sintetizado con anterioridad, 6-aminopiridin-3-carboxilato de metilo (1,93 g), trietilamina (12,8 mL) y cloruro de metileno (40 mL) se

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añadió una solución 1,0 M (13,8 mL) de cloruro de titanio (IV) en cloruro de metileno a 0 °C y la mezcla se agitó bajo una atmósfera de argón a temperatura ambiente durante 1,5 días. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción, el cloruro de metileno se eliminó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una mezcla del aceite obtenido, etanol (40 mL) y tetrahidrofurano (20 mL) se añadieron ácido acético (3,29 mL) y cianoborohidruro de sodio (3,61 g) y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción, el solvente orgánico se eliminó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 30% de acetato de etilo/hexano) para dar el compuesto objeto del título (547 mg, 12%) en forma de un sólido de color marrón pálido. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,82 - 1,35 (m, 5 H), 1,44 - 1,55 (m, 1 H), 1,56 - 1,86 (m, 3 H), 1,85 - 2,10 (m, 2 H), 2,24 (s, 3 H), 3,83 (s, 3 H), 5,02 - 5,14 (m, 1 H), 5,42 (d, J = 8,2 Hz, 1 H), 6,33 (d, J = 8,8 Hz, 1 H), 6,88 - 6,97 (m, 1 H), 7,04 - 7,10 (m, 1 H), 7,26 - 7,32 (m, 1 H), 7,90 (dd, J = 8,8, 2,4 Hz, 1 H), 8,72 (d, J = 2,4 Hz, 1 H).

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(4) ácido 6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-carboxílico

A una mezcla de 6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-carboxilato de metilo (547 mg) sintetizado con anterioridad, etanol (10 mL) y tetrahidrofurano (10 mL) se añadió solución acuosa 1 N de hidróxido de sodio (10 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo. Además, se añadió solución acuosa 1 N de hidróxido de sodio (5,00 mL) se añadió y la mezcla se agitó con calentamiento a reflujo durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (20 mL) y ácido clorhídrico 1 N (15 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración y el sólido de color marrón pálido obtenido se disolvió en acetato de etilo. La solución se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (478 mg, 90%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 - 1,41 (m, 5 H), 1,48 - 1,84 (m, 4 H), 2,01 - 2,18 (m, 2 H), 2,23 (s, 3 H), 4,47 - 4,65 (m, 1 H), 6,34 (d, J = 8,8 Hz, 1 H), 6,87 - 6,97 (m, 1 H), 7,03 - 7,10 (m, 1 H), 7,26 - 7,33 (m, 1 H), 8,08 (d, J = 8,8 Hz, 1 H), 8,70 - 8,74 (m, 1 H).

(5) 3-{[(6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil]amino}propanoato de etilo

A una mezcla de ácido 6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-carboxílico (300 mg)

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sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (181 mg), monohidrato de 1-hidroxibenzotriazol (181 mg), trietilamina (328 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (226 mg) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (366 mg, 97%) en forma de un aceite de color marrón pálido

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,36 (m, 8 H), 1,43 - 1,55 (m, 1 H), 1,57 - 1,85 (m, 3 H), 1,85 - 2,08 (m, 2 H), 2,24 (s, 3 H), 2,60 (t, J = 5,9 Hz, 2 H), 3,62 - 3,72 (m, 2 H), 4,15 (q, J = 7,1 Hz, 2 H), 5,01 - 5,12 (m, 1 H), 5,25 (d, J = 8,8 Hz, 1 H), 6,35 (d, J = 8,8 Hz, 1 H), 6,65 (t, J = 6,0 Hz, 1 H), 6,88 - 6,97 (m, 1 H), 7,03 - 7,10 (m, 1 H), 7,23 - 7,31 (m, 1 H), 7,75 (dd, J = 8,8, 2,5 Hz, 1 H), 8,48 (d, J = 2,5 Hz, 1 H).

(6) ácido 3-{[(6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil]amino}propanoico

A una mezcla de 3-{[(6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil]amino}propanoato de etilo (366 mg) sintetizado

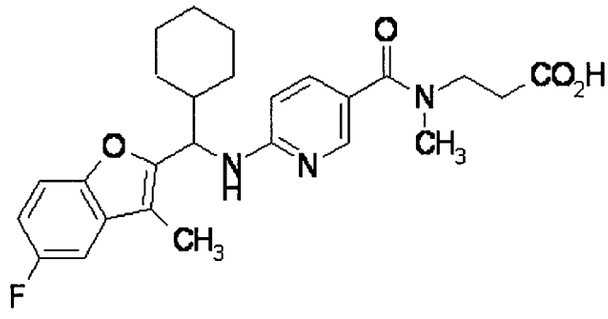
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con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante la noche y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (287 mg, 83%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 - 1,41 (m, 5 H), 1,44 - 1,55 (m, 1 H), 1,59 - 1,84 (m, 3 H), 1,97 - 2,15 (m, 2 H), 2,23 (s, 3 H), 2,55 - 2,69 (m, 2 H), 3,65 - 3,78 (m, 2 H), 4,46 (t, J = 7,8 Hz, 1 H), 6,48 (d, J = 9,1 Hz, 1 H), 6,89 - 6,99 (m, 1 H), 7,04 - 7,11 (m, 1 H), 7,27 - 7,35 (m, 1 H), 7,51 - 7,61 (m, 1 H), 8,13 (dd, J = 9,1, 2,1 Hz, 1 H), 8,22 (d, J = 2,1 Hz, 1 H), 8,25 - 8,41 (m, 1 H).

Ejemplo A52

Ácido 3-{[(6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil](metil)amino}propanoico



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(1) 3-{[(6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-carboxílico (294 mg) sintetizado en el Ejemplo A51(4), 3-(metilamino)propanoato de etilo (151 mg), monohidrato de 1-hidroxibenzotriazol (176 mg), trietilamina (322 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (221 mg) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (236 mg, 62%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,34 (m, 8 H), 1,45 - 1,57 (m, 1 H), 1,58 - 1,83 (m, 3 H), 1,84 - 2,09 (m, 2 H), 2,23 (s, 3 H), 2,63 (t, J = 7,0 Hz, 2 H), 3,05 (s, 3 H), 3,72 (t, J = 7,0 Hz, 2 H), 4,03 - 4,17 (m, 2 H), 4,97 - 5,07 (m, 1 H), 5,08 - 5,18 (m, 1 H), 6,34 (d, J = 8,6 Hz, 1 H), 6,88 - 6,97 (m, 1 H), 7,04 - 7,10 (m, 1 H), 7,23 - 7,31 (m, 1 H), 7,46 (dd, J = 8,6, 2,1 Hz, 1 H), 8,18 (d, J = 2,1 Hz, 1 H).

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(2) ácido 3-{[(6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil](metil)amino}propanoico

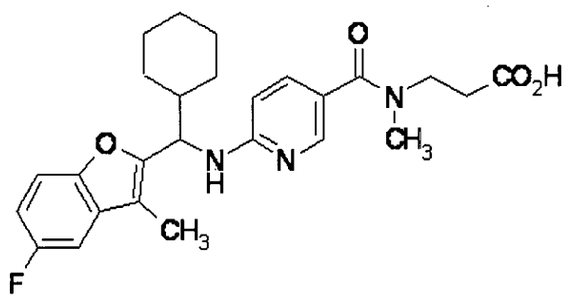
A una mezcla de 3-{[(6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil](metil)amino}propanoato de etilo (236 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL), ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido de color amarillo pálido. El sólido obtenido se recristalizó en acetato de etilo/hexano para dar el compuesto objeto del título (143 mg, 64%) en forma de cristales incoloros.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 - 1,37 (m, 5 H), 1,38 - 1,53 (m, 1 H), 1,55 - 1,82 (m, 3 H), 1,87 - 2,12 (m, 2 H), 2,20 (s, 3 H), 2,48 - 2,68 (m, 2 H), 2,99 (br s, 3 H), 3,59 - 3,79 (m, 2 H), 4,54 - 4,76 (m, 1 H), 6,34 (d, J = 8,8 Hz, 1 H), 6,86 - 6,97 (m, 1 H), 7,01 - 7,09 (m, 1 H), 7,23 - 7,34 (m, 1 H), 7,51 (d, J = 8,8 Hz, 1 H), 8,11 (br s, 1 H).

Ejemplo A53

Ácido 3-{[(6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil](metil)amino}propanoico

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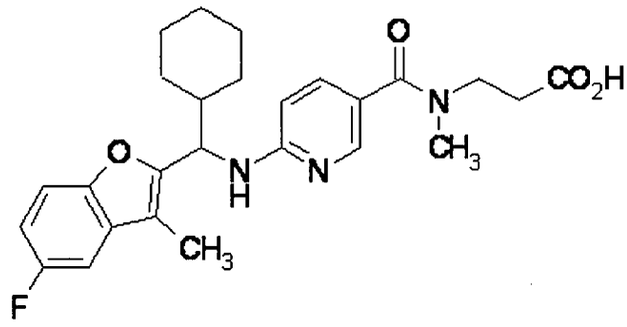
El 3-{[(6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil](metil)amino}propanoato de de etilo (4,06 g) sintetizado en el Ejemplo A52(1) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm IDx500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/2-propanol (700/300-200/800), velocidad de flujo: 60 mL/min-50 mL/min, temperatura de la columna: temperatura ambiente). La fracción que contenía una forma ópticamente activa con un tiempo de retención más corto en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (1,94 g, 99,9% ee). A una mezcla de la forma amorfa obtenida, etanol (10 mL) y tetrahidrofurano (10 mL) se añadió solución acuosa 1 N de hidróxido de litio (8 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (8 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (1,81 g, 95%, 99,9% ee) en forma de un sólido blanco.

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$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,89 - 1,28 (m, 5 H) 1,34 (d, J = 12,12 Hz, 1 H) 1,49 - 1,80 (m, 3 H) 1,80 - 2,08 (m, 2 H) 2,23 (s, 3 H) 2,50 - 2,54 (m, 2 H) 2,92 (s, 3 H) 3,53 (t, J = 7,38 Hz, 2 H) 5,15 (t, J = 8,90 Hz, 1 H) 6,56 (d, J = 8,71 Hz, 1 H) 7,05 (td, J = 9,28, 2,65 Hz, 1 H) 7,31 (dd, J = 8,71, 2,65 Hz, 1 H) 7,36 - 7,56 (m, 2 H) 8,04 (d, J = 2,27 Hz, 1 H) 12,22 (brs, 1 H).

Ejemplo A54

Ácido 3-{[(6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil](metil)amino}propanoico




El 3-{[(6-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil](metil)amino}propanoato de etilo (4,06 g) sintetizado en el Ejemplo A52(1) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm IDx500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/2-propanol (700/300-200/800), velocidad de flujo: 60 mL/min, temperatura de la columna: temperatura ambiente). La fracción que contenía una forma ópticamente activa con un tiempo de

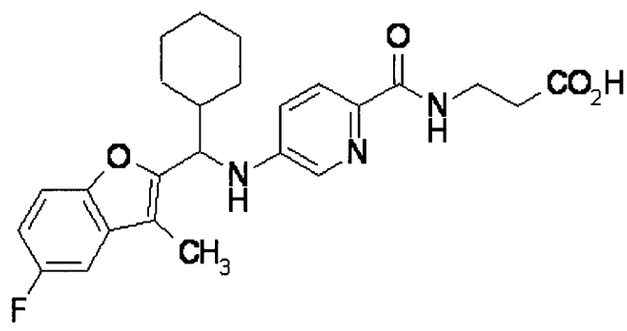
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retención más largo en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (1,96 g, 99,9% ee). A una mezcla de la forma amorfa obtenida, etanol (10 mL) y tetrahidrofurano (10 mL) se añadió solución acuosa 1 N de hidróxido de litio (8 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (8 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (1,80 g, 99%, 99,9% ee) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,89 - 1,28 (m, 5 H) 1,34 (d, J = 12,12 Hz, 1 H) 1,49 - 1,80 (m, 3 H) 1,80 - 2,08 (m, 2 H) 2,23 (s, 3 H) 2,50 - 2,54 (m, 2 H) 2,92 (s, 3 H) 3,53 (t, J = 7,38 Hz, 2 H) 5,15 (t, J = 8,90 Hz, 1 H) 6,56 (d, J = 8,71 Hz, 1 H) 7,05 (td, J = 9,28, 2,65 Hz, 1 H) 7,31 (dd, J = 8,71, 2,65 Hz, 1 H) 7,36 - 7,56 (m, 2 H) 8,04 (d, J = 2,27 Hz, 1 H) 12,22 (brs, 1 H).

Ejemplo A55

Ácido 3-{[(5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-il)carbonil]amino}propanoico



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(1) 5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-carboxilato de metilo

A una solución (15 mL) de ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metanol (1,50 g) sintetizado en el Ejemplo A37(2) en tolueno se añadió cloruro de tionilo (625 µL) y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se vertió en solución saturada acuosa de carbonato ácido de sodio helada y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite marrón. A una mezcla del aceite obtenido, 5-aminopiridin-2-carboxilato de metilo (957 mg), yoduro de sodio (1,71 g) y N,N-dimetilformamida (15 mL) se añadió carbonato de sodio (1,21 g) y la mezcla se agitó a 80 °C durante la noche. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (10 - 50% de acetato de etilo/hexano) para dar el compuesto objeto del título (909 mg, 40%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,37 (m, 5 H), 1,46 - 1,57 (m, 1 H), 1,60 - 2,00 (m, 4 H), 2,02 - 2,14 (m, 1 H), 2,23 (s, 3 H), 3,90 (s, 3 H), 4,39 (t, J = 8,2 Hz, 1 H), 4,70

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(d, J = 8,2 Hz, 1 H), 6,84 (dd, J = 8,6, 3,0 Hz, 1 H), 6,89 - 6,97 (m, 1 H), 7,04 - 7,10 (m, 1 H), 7,22 - 7,30 (m, 1 H), 7,88 (d, J = 8,6 Hz, 1 H), 8,08 (d, J = 3,0 Hz, 1 H).

(2) ácido 5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-carboxílico

A una mezcla de 5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-carboxilato de metilo (909 mg) sintetizado con anterioridad, etanol (20 mL) y tetrahidrofurano (20 mL) se añadió solución acuosa 1 N de hidróxido de sodio (20 mL) y la mezcla se agitó con calentamiento a reflujo durante 5 h y se concentró a presión reducida. El ácido clorhídrico 1 N (20 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con hexano para dar el compuesto objeto del título (751 mg, 86%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,39 (m, 5 H), 1,46 - 1,60 (m, 1 H), 1,62 - 2,02 (m, 4 H), 2,02 - 2,15 (m, 1 H), 2,25 (s, 3 H), 4,41 (t, J = 7,9 Hz, 1 H), 4,72 - 4,83 (m, 1 H), 6,90 - 7,00 (m, 2 H), 7,07 - 7,13 (m, 1 H), 7,24 - 7,33 (m, 1 H), 7,91 - 7,98 (m, 2 H).

(3) 3-{[(5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-il)carbonil]amino}propanoato de etilo

A una mezcla de ácido 5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-carboxílico (300 mg) sintetizado con anterioridad, clorhidrato de éster etílico de

β-alanina (181 mg), monohidrato de 1-hidroxibenzotriazol (181 mg), trietilamina (328 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (226 mg) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (361 mg, 96%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,39 (m, 8 H), 1,46 - 2,00 (m, 5 H), 2,03 - 2,14 (m, 1 H), 2,24 (s, 3 H), 2,60 (t, J = 6,2 Hz, 2 H), 3,64 - 3,72 (m, 2 H), 4,15 (q, J = 7,1 Hz, 2 H), 4,34 - 4,42 (m, 1 H), 4,45 - 4,52 (m, 1 H), 6,86 - 6,98 (m, 2 H), 7,05 - 7,10 (m, 1 H), 7,24 - 7,30 (m, 1 H), 7,87 - 7,93 (m, 2 H), 8,06 - 8,13 (m, 1 H).

(4) ácido 3-{[(5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-il)carbonil]amino}propanoico

A una mezcla de 3-{[(5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-il)carbonil]amino}propanoato de etilo (361 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se

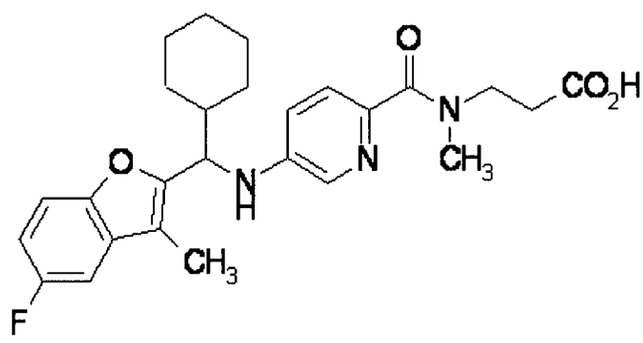
1274

concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (324 mg, 95%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,36 (m, 5 H), 1,45 - 1,56 (m, 1 H), 1,61 - 2,00 (m, 4 H), 2,01 - 2,12 (m, 1 H), 2,22 (s, 3 H), 2,65 (t, J = 6,1 Hz, 2 H), 3,64 - 3,75 (m, 2 H), 4,37 (d, J = 8,0 Hz, 1 H), 6,85 - 6,99 (m, 2 H), 7,03 - 7,10 (m, 1 H), 7,23 - 7,30 (m, 1 H), 7,86 - 7,94 (m, 2 H), 8,14 (t, J = 6,2 Hz, 1 H).

Ejemplo A56

Ácido 3-{[(5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoico




(1) 3-{[(5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-carboxílico (300 mg) sintetizado en el Ejemplo A55(2), 3-(metilamino)propanoato de

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etilo (155 mg), monohidrato de 1-hidroxibenzotriazol (181 mg), trietilamina (328 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (226 mg) y la mezcla se agitó a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (20 - 60% de acetato de etilo/hexano) para dar el compuesto objeto del título (318 mg, 82%) en forma de un aceite amarillo pálido. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,38 (m, 8 H), 1,46 - 1,57 (m, 1 H), 1,60 - 1,99 (m, 4 H), 2,03 - 2,16 (m, 1 H), 2,22 (s, 3 H), 2,63 - 2,78 (m, 2 H), 3,00 - 3,21 (m, 3 H), 3,69 - 3,87 (m, 2 H), 4,01 - 4,19 (m, 2 H), 4,32 - 4,40 (m, 1 H), 4,41 - 4,49 (m, 1 H), 6,84 - 6,98 (m, 2 H), 7,04 - 7,11 (m, 1 H), 7,24 - 7,31 (m, 1 H), 7,44 - 7,59 (m, 1 H), 7,88 - 7,95 (m, 1 H).

(2) ácido 3-{[(5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoico

A una mezcla de 3-{[(5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoato de etilo (318 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de

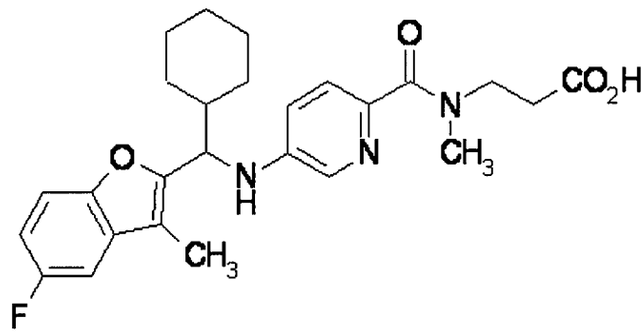
1276

sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (262 mg, 87%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,37 (m, 5 H), 1,46 - 1,56 (m, 1 H), 1,60 - 1,99 (m, 4 H), 2,03 - 2,13 (m, 1 H), 2,23 (s, 3 H), 2,68 - 2,89 (m, 2 H), 3,09 (br s, 3 H), 3,77 (t, J = 6,8 Hz, 2 H), 4,36 (d, J = 8,3 Hz, 1 H), 6,87 - 6,99 (m, 2 H), 7,05 - 7,11 (m, 1 H), 7,24 - 7,32 (m, 1 H), 7,48 - 7,66 (m, 1 H), 7,90 - 8,00 (m, 1 H).

Ejemplo A57

Ácido 3-{[(5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoico




El 3-{[(5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoato de etilo (5,83 g) sintetizado en el Ejemplo A56(1) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm ID×500 mmL, fabricada por

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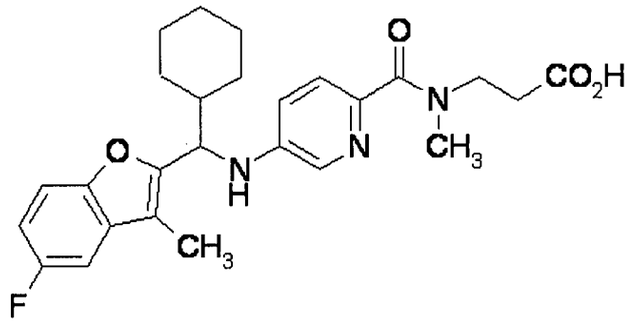
Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (500/500), velocidad de flujo: 60 mL/min, temperatura de la columna: temperatura ambiente). La fracción que contenía una forma ópticamente activa con un tiempo de retención más corto en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (2,90 g, 99,9%ee). A una mezcla de la forma amorfa obtenida, etanol (10 mL) y tetrahidrofurano (10 mL) se añadió solución acuosa 1 N de hidróxido de litio (12 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (30 mL) y ácido clorhídrico 1 N (12 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (2,67 g, 99%, 99,9% ee) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,98 - 1,29 (m, 5 H) 1,30 - 1,39 (m, 1 H) 1,63 (brs, 2 H) 1,75 (d, J = 11,36 Hz, 1 H) 1,82 - 2,00 (m, 1 H) 2,09 (d, J = 11,74 Hz, 1 H) 2,25 (s, 3 H) 2,53 - 2,66 (m, 2 H) 2,88 - 3,03 (m, 3 H) 3,32 (br s, 2 H) 4,51 (t, J = 8,33 Hz, 1 H) 6,80 (d, J = 8,3 Hz, 1 H) 6,96 (dd, J = 8,71, 2,65 Hz, 1 H) 7,05 (td, J = 9,28, 2,65 Hz, 1 H) 7,26 - 7,39 (m, 2 H) 7,47 (dd, J = 8,90, 3,98 Hz, 1 H) 7,95 (d, J = 2,27 Hz, 1 H) 12,26 (br s, 1 H).

Ejemplo A58

Ácido 3-{[(5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoico

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El 3-{[(5-{[ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoato de etilo (5,83 g) sintetizado en el Ejemplo A56(1) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm IDx500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (500/500), velocidad de flujo: 60 mL/min, temperatura de la columna: temperatura ambiente). La fracción que contenía una forma ópticamente activa con un tiempo de retención más largo en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (2,82 g, 99,9% ee). A una mezcla de la forma amorfa obtenida, etanol (10 mL) y tetrahidrofurano (10 mL) se añadió solución acuosa 1 N de hidróxido de litio (12 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (30 mL) y ácido clorhídrico 1 N (12 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (2,64 g, 97%, 99,9% ee) en forma de un sólido blanco.

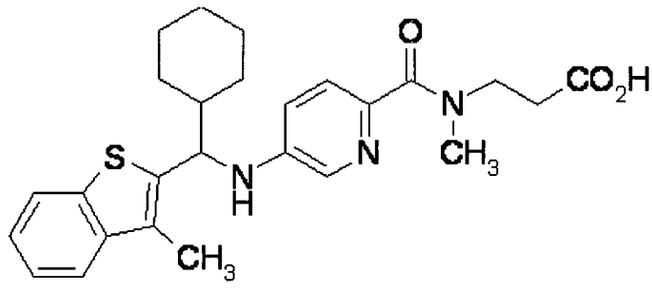
$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,98 - 1,29 (m, 5 H) 1,30 - 1,39 (m, 1 H) 1,63 (brs, 2 H) 1,75 (d, J = 11,36 Hz, 1 H)

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1,82 - 2,00 (m, 1 H) 2,09 (d, J = 11,74 Hz, 1 H) 2,25 (s, 3 H) 2,53 - 2,66 (m, 2 H) 2,88 - 3,03 (m, 3 H) 3,32 (br s, 2 H) 4,51 (t, J = 8,33 Hz, 1 H) 6,80 (d, J = 8,33 Hz, 1 H) 6,96 (dd, J = 8,71, 2,65 Hz, 1 H) 7,05 (td, J = 9,28, 2,65 Hz, 1 H) 7,26 - 7,39 (m, 2 H) 7,47 (dd, J = 8,90, 3,98 Hz, 1 H) 7,95 (d, J = 2,27 Hz, 1 H) 12,26 (br s, 1 H).

Ejemplo A59

Ácido 3-{[(5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoico




(1) 5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-carboxilato de metilo

A una mezcla de 2-[cloro(ciclohexil)metil]-3-metil-1-benzotiofeno (664 mg) sintetizado en el Ejemplo A10(2), 5-aminopiridin-2-carboxilato de metilo (362 mg), yoduro de sodio (714 mg) y N,N-dimetilformamida (10 mL) se añadió carbonato de sodio (505 mg) y la mezcla se agitó a 80 °C durante la noche. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por

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cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (460 mg, 49%) en forma de un sólido amarillo pálido.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 - 1,37 (m, 5 H), 1,54 - 1,88 (m, 5 H), 2,07 - 2,18 (m, 1 H), 2,47 (s, 3 H), 3,88 (s, 3 H), 4,54 - 4,68 (m, 2 H), 6,78 (dd, J = 8,6, 2,7 Hz, 1 H), 7,22 - 7,30 (m, 1 H), 7,31 - 7,38 (m, 1 H), 7,63 (d, J = 8,0 Hz, 1 H), 7,68 (d, J = 8,0 Hz, 1 H), 7,84 (d, J = 8,6 Hz, 1 H), 8,05 (d, J = 2,7 Hz, 1 H).

(2) ácido 5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-carboxílico

A una mezcla de 5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-carboxilato de metilo (460 mg) sintetizado con anterioridad, etanol (5 mL) y tetrahidrofurano (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (5,00 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (10 mL), el ácido clorhídrico 1 N (5,00 mL) se añadió a 0 °C y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (452 mg, cuantitativo) en forma de un sólido de color marrón pálido.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 - 1,38 (m, 5 H), 1,56 - 1,90 (m, 5 H), 2,08 - 2,18 (m, 1 H), 2,50 (s, 3 H), 4,56 - 4,64 (m, 1 H), 4,68 - 4,77 (m, 1 H), 6,88 (dd, J = 8,7, 2,6 Hz, 1 H), 7,25 - 7,33 (m, 1 H), 7,34 - 7,41 (m, 1 H), 7,66

1281

(d, J = 7,4 Hz, 1 H), 7,71 (d, J = 7,7 Hz, 1 H), 7,86 - 7,93 (m, 2 H).

(3) 3-{[(5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-carboxílico (200 mg) sintetizado con anterioridad, 3-(metilamino)propanoato de etilo (104 mg), monohidrato de 1-hidroxibenzotriazol (121 mg), trietilamina (220 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (151 mg) y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (141 mg, 54%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 - 1,35 (m, 8 H), 1,55 - 1,88 (m, 5 H), 2,06 - 2,17 (m, 1 H), 2,46 (s, 3 H), 2,61 - 2,76 (m, 2 H), 2,98 - 3,18 (m, 3 H), 3,69 - 3,87 (m, 2 H), 3,98 - 4,18 (m, 2 H), 4,39 (d, J = 6,0 Hz, 1 H), 4,51 - 4,58 (m, 1 H), 6,81 (dd, J = 8,5, 2,7 Hz, 1 H), 7,23 - 7,30 (m, 1 H), 7,31 - 7,38 (m, 1 H), 7,39 - 7,55 (m, 1 H), 7,63 (d, J =

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7,4 Hz, 1 H), 7,70 (d, J = 7,7 Hz, 1 H), 7,84 - 7,91 (m, 1 H).

(4) ácido 3-{[(5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoico

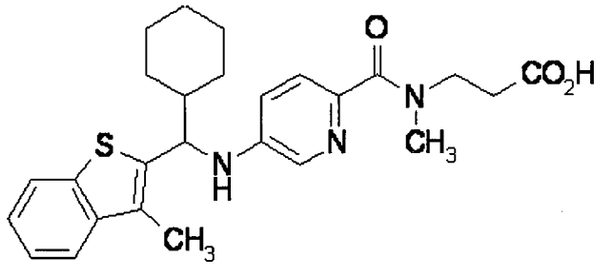
A una mezcla de 3-{[(5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoato de etilo (141 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 30 min y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (112 mg, 84%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,01 - 1,37 (m, 5 H), 1,54 - 1,89 (m, 5 H), 2,06 - 2,18 (m, 1 H), 2,47 (s, 3 H), 2,73 - 2,90 (m, 2 H), 3,08 (br s, 3 H), 3,76 (t, J = 6,4 Hz, 2 H), 4,55 (d, J = 8,0 Hz, 1 H), 6,83 - 6,93 (m, 1 H), 7,23 - 7,33 (m, 1 H), 7,33 - 7,41 (m, 1 H), 7,47 - 7,63 (m, 1 H), 7,65 (d, J = 7,6 Hz, 1 H), 7,71 (d, J = 7,6 Hz, 1 H), 7,85 - 7,94 (m, 1 H).

Ejemplo A60

Ácido 3-{[(5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoico

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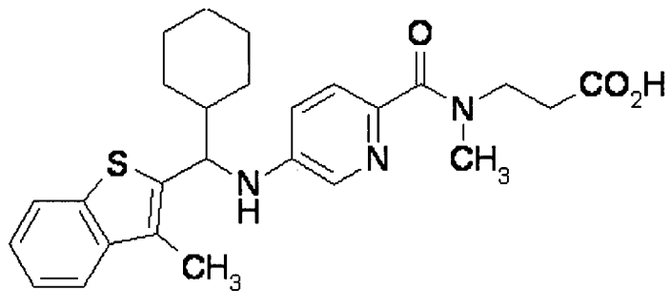
El 3-{[(5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoato de etilo (9,31 g) sintetizado en el Ejemplo A59(3) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm IDx500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/2-propanol (700/300-200/800), velocidad de flujo: 60 mL/min-50 mL/min, temperatura de la columna: temperatura ambiente). La fracción que contenía una forma ópticamente activa con un tiempo de retención más corto en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (4,67 g, 99,9% ee). A una mezcla de la forma amorfa obtenida, etanol (20 mL) y tetrahidrofurano (20 mL) se añadió solución acuosa 1 N de hidróxido de litio (20 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (20 mL) y ácido clorhídrico 1 N (20 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (4,17 g, 99%, 99,9% ee) en forma de un sólido blanco.

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$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 1,00 - 1,32 (m, 5 H) 1,37 - 1,51 (m, 1 H) 1,52 - 1,84 (m, 4 H) 2,07 - 2,20 (m, 1 H) 2,46 (s, 3 H) 2,50 - 2,57 (m, 2 H) 2,87 - 3,01 (m, 3 H) 3,27 - 3,36 (m, 5 H) 3,43 - 3,68 (m, 2 H) 4,63 (t, J = 7,38 Hz, 1 H) 6,87 (d, J = 6,82 Hz, 2 H) 7,19 - 7,41 (m, 3 H) 7,69 (d, J = 7,19 Hz, 1 H) 7,79 (d, J = 7,57 Hz, 1 H) 7,89 (d, J = 2,65 Hz, 1 H) 12,16 (brs, 1 H).

Ejemplo A61

Ácido 3-{[(5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoico



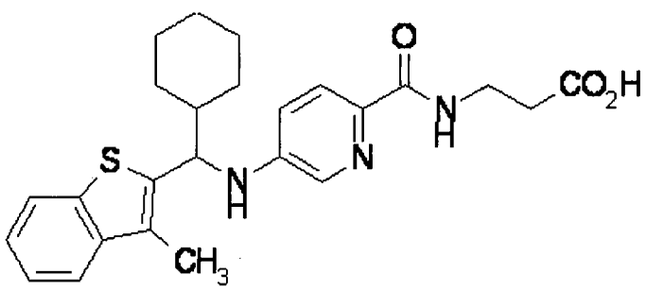

El 3-{[(5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-il)carbonil](metil)amino}propanoato de etilo (9,31 g) sintetizado en el Ejemplo A59(3) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm ID×500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/2-propanol (700/300-200/800), velocidad de flujo: 60 mL/min-50 mL/min, temperatura de la columna: temperatura ambiente). La fracción que contenía una forma ópticamente activa con un

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tiempo de retención más largo en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (4,52 g, 99,9% ee). A una mezcla de la forma amorfa obtenida, etanol (20 mL) y tetrahidrofurano (20 mL) se añadió solución acuosa 1 N de hidróxido de litio (20 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (20 mL) y ácido clorhídrico 1 N (20 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (4,12 g, 98%, 99,9% ee) en forma de un sólido blanco. $^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 1,00 - 1,32 (m, 5 H) 1,37 - 1,51 (m, 1 H) 1,52 - 1,84 (m, 4 H) 2,07 - 2,20 (m, 1 H) 2,46 (s, 3 H) 2,50 - 2,57 (m, 2 H) 2,87 - 3,01 (m, 3 H) 3,27 - 3,36 (m, 5 H) 3,43 - 3,68 (m, 2 H) 4,63 (t, J = 7,38 Hz, 1 H) 6,87 (d, J = 6,82 Hz, 2 H) 7,19 - 7,41 (m, 3 H) 7,69 (d, J = 7,19 Hz, 1 H) 7,79 (d, J = 7,57 Hz, 1 H) 7,89 (d, J = 2,65 Hz, 1 H) 12,16 (brs, 1 H).

Ejemplo A62

Ácido 3-{[(5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-il)carbonil]amino}propanoico



1286

(1) 3-{[(5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-il)carbonil]amino}propanoato de etilo

A una mezcla de ácido 5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-carboxílico (247 mg) sintetizado en el Ejemplo A59(2), clorhidrato de éster etílico de β-alanina (149 mg), monohidrato de 1-hidroxibenzotriazol (149 mg), trietilamina (270 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (186 mg) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (274 mg, 88%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,35 (m, 8 H), 1,54 - 1,88 (m, 5 H), 2,06 - 2,18 (m, 1 H), 2,47 (s, 3 H), 2,58 (t, J = 6,3 Hz, 2 H), 3,61 - 3,71 (m, 2 H), 4,13 (q, J = 7,1 Hz, 2 H), 4,48 - 4,60 (m, 2 H), 6,80 - 6,87 (m, 1 H), 7,22 - 7,30 (m, 1 H), 7,31 - 7,38 (m, 1 H), 7,64 (d, J = 7,4 Hz, 1 H), 7,69 (d, J = 8,0 Hz, 1 H), 7,83 - 7,88 (m, 2 H), 8,07 (t, J = 6,3 Hz, 1 H).

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(2) ácido 3-{[(5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-il)carbonil]amino}propanoico

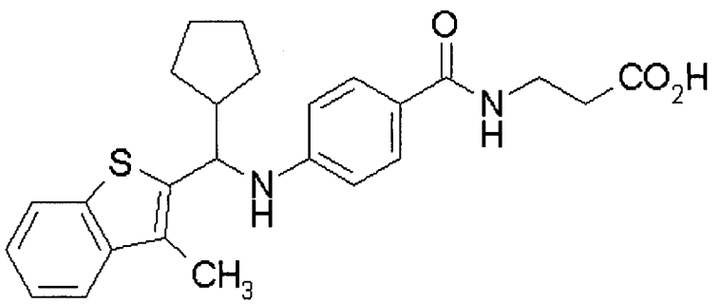
A una mezcla de 3-{[(5-{[ciclohexil(3-metil-1-benzotiofen-2-il)metil]amino}piridin-2-il)carbonil]amino}propanoato de etilo (274 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (235 mg, 91%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,36 (m, 5 H), 1,54 - 1,89 (m, 5 H), 2,06 - 2,18 (m, 1 H), 2,47 (s, 3 H), 2,64 (t, J = 6,0 Hz, 2 H), 3,61 - 3,73 (m, 2 H), 4,56 (d, J = 7,9 Hz, 1 H), 6,84 (dd, J = 8,5, 2,4 Hz, 1 H), 7,22 - 7,31 (m, 1 H), 7,31 - 7,40 (m, 1 H), 7,64 (d, J = 7,9 Hz, 1 H), 7,69 (d, J = 7,9 Hz, 1 H), 7,82 - 7,91 (m, 2 H), 8,11 (t, J = 6,0 Hz, 1 H).

Ejemplo A63

Ácido 3-{[(4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}fenil)carbonil]amino}propanoico

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(1) ciclopentil(3-metil-1-benzotiofen-2-il)metanona

A una mezcla de 3-metil-1-benzotiofeno (1,00 g), cloruro de ciclopentancarbonilo (903 µL) y nitrometano (10 mL) se añadió cloruro de aluminio (1,35 g) a 0 °C y la mezcla se agitó durante 1,5 h. Se añadió agua para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de NH-gel de sílice (acetato de etilo) para dar el compuesto objeto del título (1,54 g, 93%) en forma de un aceite de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,60 - 1,84 (m, 4 H), 1,92 - 2,03 (m, 4 H), 2,78 (s, 3 H), 3,48 - 3,60 (m, 1 H), 7,40 - 7,52 (m, 2 H), 7,81 - 7,91 (m, 2 H).

(2) 4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}benzoato de metilo

A una mezcla de ciclopentil(3-metil-1-benzotiofen-2-il)metanona (1,54 g) sintetizada con anterioridad, 4-aminobenzoato de metilo (1,05 g), trietilamina (7,02 mL) y cloruro de metileno (30 mL) se añadió cloruro de titanio (IV)

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(829 µL) y la mezcla se agitó bajo una atmósfera de argón a temperatura ambiente durante 3 días. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción, el cloruro de metileno se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (30 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (721 µL) y cianoborohidruro de sodio (792 mg) y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción, el solvente orgánico se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 30% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,56 g, 65%) en forma de un sólido anaranjado.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,30 - 1,44 (m, 1 H), 1,45 - 1,82 (m, 6 H), 1,90 - 2,06 (m, 1 H), 2,28 - 2,46 (m, 1 H), 2,50 (s, 3 H), 3,79 (s, 3 H), 4,47 - 4,56 (m, 1 H), 4,62 (d, J = 9,1 Hz, 1 H), 6,51 (d, J = 9,1 Hz, 2 H), 7,22 - 7,29 (m, 1 H), 7,31 - 7,37 (m, 1 H), 7,61 - 7,66 (m, 1 H), 7,67 - 7,72 (m, 1 H), 7,76 (d, J = 9,1 Hz, 2 H).

(3) ácido 4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}benzoico

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A una mezcla de 4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}benzoato de metilo (1,56 g) sintetizado con anterioridad, tetrahidrofurano (20 mL) y etanol (20 mL) se añadió solución acuosa 1 N de hidróxido de sodio (20,0 mL) y la mezcla se agitó con calentamiento a reflujo durante 4 h y se concentró a presión reducida. El residuo se disolvió en agua (40 mL) y ácido clorhídrico 1 N (20,0 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración y el sólido de color marrón pálido obtenido se disolvió en acetato de etilo. La solución se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (1,42 g, 95%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,30 - 1,45 (m, 1 H), 1,45 - 1,82 (m, 6 H), 1,90 - 2,05 (m, 1 H), 2,27 - 2,45 (m, 1 H), 2,50 (s, 3 H), 4,63 (d, J = 9,1 Hz, 1 H), 6,52 (d, J = 8,8 Hz, 2 H), 7,22 - 7,29 (m, 1 H), 7,31 - 7,38 (m, 1 H), 7,61 - 7,66 (m, 1 H), 7,67 - 7,71 (m, 1 H), 7,80 (d, J = 8,8 Hz, 2 H).

(4) 3-{[(4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}benzoico (300 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (189 mg), monohidrato de 1-hidroxibenzotriazol (188 mg), trietilamina (343 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (236 mg) y la mezcla se agitó

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a temperatura ambiente durante 5 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (331 mg, 87%) en forma de un aceite de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,23 (t, J = 7,1 Hz, 3 H), 1,30 - 1,45 (m, 1 H), 1,45 - 1,81 (m, 6 H), 1,90 - 2,07 (m, 1 H), 2,27 - 2,47 (m, 1 H), 2,50 (s, 3 H), 2,56 (t, J = 5,8 Hz, 2 H), 3,59 - 3,68 (m, 2 H), 4,12 (q, J = 7,1 Hz, 2 H), 4,42 (d, J = 5,7 Hz, 1 H), 4,60 (dd, J = 9,1, 5,7 Hz, 1 H), 6,48 - 6,60 (m, 3 H), 7,21 - 7,29 (m, 1 H), 7,30 - 7,37 (m, 1 H), 7,50 (d, J = 8,8 Hz, 2 H), 7,61 - 7,65 (m, 1 H), 7,66 - 7,72 (m, 1 H).

(5) ácido 3-{[(4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}fenil)carbonil]amino}propanoico

A una mezcla de 3-{[(4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo (331 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 1,5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El

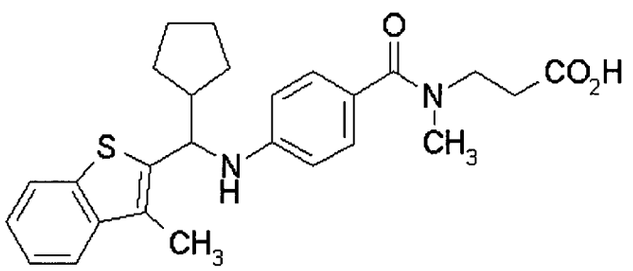
1292

precipitado resultante se recogió por filtración para dar el compuesto objeto del título (276 mg, 89%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,28 - 1,43 (m, 1 H), 1,44 - 1,80 (m, 6 H), 1,89 - 2,03 (m, 1 H), 2,25 - 2,43 (m, 1 H), 2,48 (s, 3 H), 2,56 (t, J = 5,3 Hz, 2 H), 3,52 - 3,63 (m, 2 H), 4,58 (d, J = 9,0 Hz, 1 H), 6,45 - 6,60 (m, 3 H), 7,20 - 7,28 (m, 1 H), 7,29 - 7,37 (m, 1 H), 7,46 (d, J = 8,3 Hz, 2 H), 7,62 (d, J = 7,5 Hz, 1 H), 7,68 (d, J = 7,9 Hz, 1 H).

Ejemplo A64

Ácido 3-{[(4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) 3-{[(4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}benzoico (300 mg) sintetizado en el Ejemplo A63(3), 3-(metilamino)propanoato de etilo (161 mg), monohidrato de 1-hidroxibenzotriazol (188 mg), trietilamina (343 µL) y N,N-dimetilformamida (10 mL) se

añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (236 mg) y la mezcla se agitó a temperatura ambiente durante 5 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (228 mg, 58%) en forma de un aceite de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,21 (t, J = 7,2 Hz, 3 H), 1,31 - 1,44 (m, 1 H), 1,45 - 1,83 (m, 6 H), 1,89 - 2,04 (m, 1 H), 2,28 - 2,43 (m, 1 H), 2,49 (s, 3 H), 2,59 (t, J = 7,1 Hz, 2 H), 2,98 (s, 3 H), 3,68 (t, J = 7,1 Hz, 2 H), 4,09 (q, J = 7,2 Hz, 2 H), 4,27 - 4,33 (m, 1 H), 4,53 - 4,61 (m, 1 H), 6,51 (d, J = 8,5 Hz, 2 H), 7,17 (d, J = 8,5 Hz, 2 H), 7,22 - 7,29 (m, 1 H), 7,31 - 7,38 (m, 1 H), 7,61 - 7,66 (m, 1 H), 7,68 - 7,73 (m, 1 H).

(2) ácido 3-{[(4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

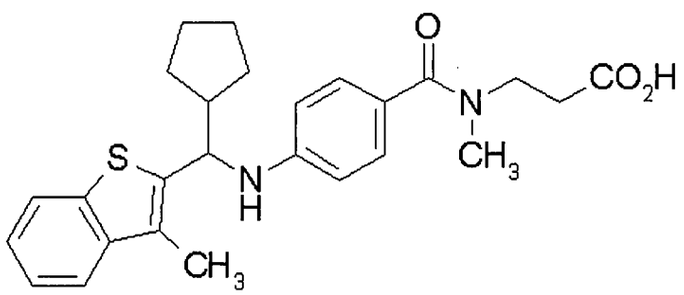
A una mezcla de 3-{[(4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (228 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a

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temperatura ambiente durante 3 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (198 mg, 92%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,28 - 1,44 (m, 1 H), 1,44 - 1,79 (m, 6 H), 1,89 - 2,04 (m, 1 H), 2,26 - 2,43 (m, 1 H), 2,49 (s, 3 H), 2,62 (t, J = 6,2 Hz, 2 H), 2,98 (s, 3 H), 3,66 (t, J = 6,2 Hz, 2 H), 4,57 (d, J = 9,0 Hz, 1 H), 6,51 (d, J = 8,5 Hz, 2 H), 7,20 (d, J = 8,5 Hz, 2 H), 7,23 - 7,30 (m, 1 H), 7,31 - 7,38 (m, 1 H), 7,64 (d, J = 7,5 Hz, 1 H), 7,71 (d, J = 7,5 Hz, 1 H).

Ejemplo A65

Ácido 3-{[(4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




El 3-{[(4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (19,7 g) sintetizado en el Ejemplo A64(1) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm ID×500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (500/500),

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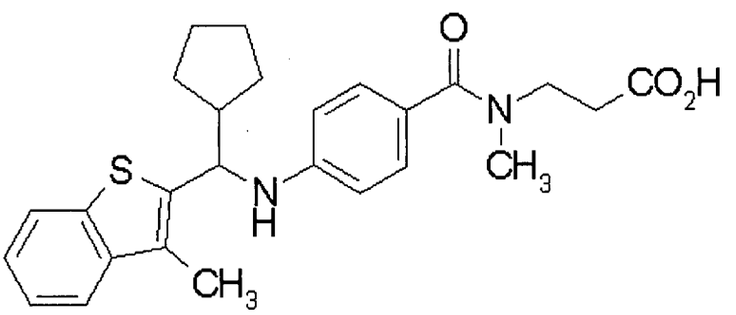
velocidad de flujo: 60 mL/min, temperatura de la columna: temperatura ambiente). La fracción que contenía una forma ópticamente activa con un tiempo de retención más corto en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (8,75 g, 99,9% ee). A una mezcla de la forma amorfa obtenida, etanol (100 mL) y tetrahidrofurano (100 mL) se añadió solución acuosa 1 N de hidróxido de sodio (30 mL) y la mezcla se agitó a temperatura ambiente durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (200 mL) y ácido clorhídrico 1 N (30 mL) se añadió a 0 °C y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (7,54 g, 41%, 99,9% ee) en forma de un sólido blanco. El sólido obtenido se recristalizó en etanol/agua para dar cristales incoloros.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,28 - 1,44 (m, 1 H), 1,44 - 1,79 (m, 6 H), 1,89 - 2,04 (m, 1 H), 2,26 - 2,43 (m, 1 H), 2,49 (s, 3 H), 2,62 (t, J = 6,2 Hz, 2 H), 2,98 (s, 3 H), 3,66 (t, J = 6,2 Hz, 2 H), 4,57 (d, J = 9,0 Hz, 1 H), 6,51 (d, J = 8,5 Hz, 2 H), 7,20 (d, J = 8,5 Hz, 2 H), 7,23 - 7,30 (m, 1 H), 7,31 - 7,38 (m, 1 H), 7,64 (d, J = 7,5 Hz, 1 H), 7,71 (d, J = 7,5 Hz, 1 H).

Ejemplo A66

Ácido 3-{[(4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

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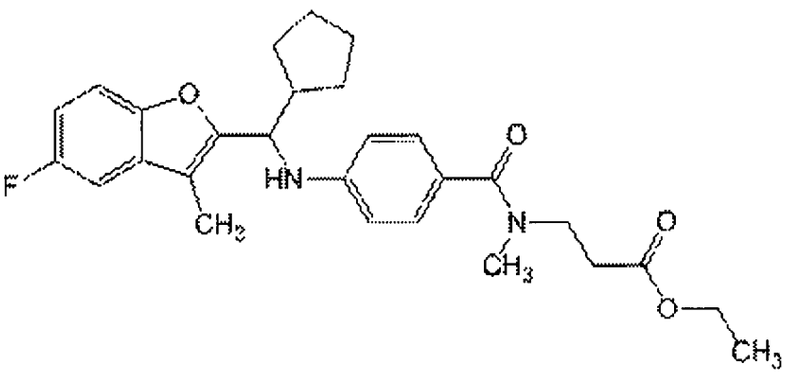
El 3-{[(4-{[ciclopentil(3-metil-1-benzotiofen-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (19,7 g) sintetizado en el Ejemplo A64(1) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50 mm IDx500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (500/500), velocidad de flujo: 60 mL/min, temperatura de la columna: temperatura ambiente). La fracción que contenía una forma ópticamente activa con un tiempo de retención más largo en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar una forma amorfa (8,95 g, 99,9% ee). A una mezcla de la forma amorfa obtenida, etanol (100 mL) y tetrahidrofurano (100 mL) se añadió solución acuosa 1 N de hidróxido de sodio (30 mL) y la mezcla se agitó a temperatura ambiente durante 3 h y se concentró a presión reducida. El residuo se disolvió en agua (200 mL) y ácido clorhídrico 1 N (35 mL) se añadió a 0 °C y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se

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concentró a presión reducida para dar el compuesto objeto del título (8,06 g, 43%, 99,9% ee) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,28 - 1,44 (m, 1 H), 1,44 - 1,79 (m, 6 H), 1,89 - 2,04 (m, 1 H), 2,26 - 2,43 (m, 1 H), 2,49 (s, 3 H), 2,62 (t, J = 6,2 Hz, 2 H), 2,98 (s, 3 H), 3,66 (t, J = 6,2 Hz, 2 H), 4,57 (d, J = 9,0 Hz, 1 H), 6,51 (d, J = 8,5 Hz, 2 H), 7,20 (d, J = 8,5 Hz, 2 H), 7,23 - 7,30 (m, 1 H), 7,31 - 7,38 (m, 1 H), 7,64 (d, J = 7,5 Hz, 1 H), 7,71 (d, J = 7,5 Hz, 1 H).

Ejemplo A67

3-{[(4-{[ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo




(1) ácido (2-acetil-4-fluorofenoxi)acético

Una solución de 5'-fluoro-2'-hidroxiacetofenona (25,0 g), bromoacetato de metilo (27,2 g), carbonato de potasio (33,6 g) en N,N-dimetilformamida (250 mL) se agitó a temperatura ambiente durante 1,5 h. El material insoluble se filtró, ácido clorhídrico 1 N se añadió al filtrado y la mezcla se extrajo con acetato de etilo. El extracto se lavó

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con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite marrón. Tetrahidrofurano (300 mL), etanol (300 mL) y solución acuosa 1 N de hidróxido de sodio (300 mL) se añadieron al aceite obtenido y la mezcla se agitó a temperatura ambiente durante 30 min. El solvente se concentró a presión reducida, el ácido clorhídrico 1 N (300 mL) se añadió y los cristales resultantes se recogieron por filtración. Los cristales se disolvieron en acetato de etilo, se secaron sobre sulfato de magnesio y se concentraron a presión reducida para dar el compuesto del título (23,7 g, 69%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,68 (s, 3 H), 4,75 (s, 2 H), 6,86 - 7,03 (m, 1 H), 7,13 - 7,30 (m, 1 H), 7,43 - 7,60 (m, 1 H).

(2) 5-fluoro-3-metil-1-benzofurano

Una mezcla de ácido (2-acetil-4-fluorofenoxi)acético (22,94 g) sintetizado con anterioridad, acetato de sodio (44,38 g) y anhídrido acético (200 mL) se agitó a 110 °C durante 15 h. La mezcla de reacción se enfrió hasta temperatura ambiente, se añadió agua y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (sílice NH, hexano) para dar el compuesto del título (14,73 g, 91%) en forma de un aceite amarillo.

1299

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,20 (s, 3 H), 6,91 - 7,03 (m, 1 H), 7,15 (dd, J = 8,3, 2,7 Hz, 1 H), 7,35 (dd, J = 8,7, 4,2 Hz, 1 H), 7,42 (s, 1 H).

(3) ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metanona

A una solución de 5-fluoro-3-metil-1-benzofurano (2,0 g) sintetizado con anterioridad, cloruro de ciclopentancarbonilo (1,94 g) en nitrometano (40 mL) se añadió cloruro de aluminio (anhidro) (2,66 g) a 0 °C y la mezcla se agitó durante 3 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 95:5, v/v) para dar el compuesto del título (2,11 g, 64%) como una forma amorfa incolora.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,67 - 2,09 (m, 8 H), 2,57 (s, 3 H), 3,64 - 3,91 (m, 1 H), 7,10 - 7,23 (m, 1 H), 7,25 - 7,31 (m, 1 H), 7,38 - 7,53 (m, 1 H).

(4) ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metanol

Ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metanona (27,15 g) sintetizada con anterioridad se disolvió en un solvente mixto de metanol (40 mL)-tetrahidrofurano (240 mL) y se añadió tetraborohidrato de sodio (90%, 5,5 g) a 0 °C. La mezcla de reacción se agitó a 0 °C durante 2 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después

1300

de filtrar, el filtrado se concentró para dar el compuesto del título (29,26 g, 100%) en forma de un aceite amarillo. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,04 - 1,20 (m, 1 H), 1,42 - 1,77 (m, 6 H), 1,92 - 2,02 (m, 2 H), 2,21 (s, 3 H), 2,42 - 2,60 (m, 1 H), 4,56 (dd, J = 9,3, 5,9 Hz, 1 H), 6,97 (td, J = 9,1, 2,7 Hz, 1 H), 7,11 (dd, J = 8,7, 2,7 Hz, 1 H), 7,33 (dd, J = 8,9, 4,0 Hz, 1 H).

(5) 3-{[(4-{[ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

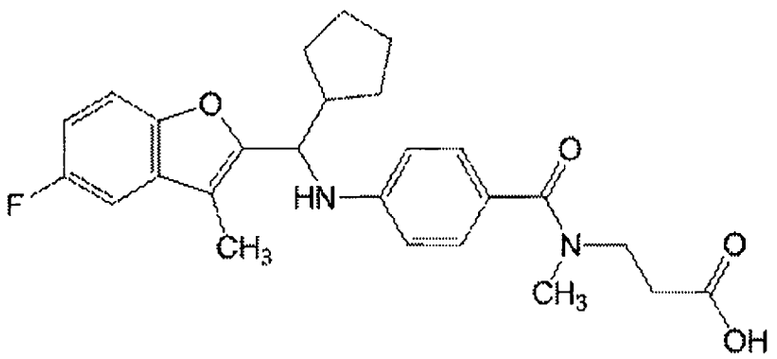
A una solución de ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metanol (27,31 g) obtenida con anterioridad en tetrahidrofurano (200 mL) se añadió cloruro de tionilo (12,0 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 2 h. A la mezcla de reacción se añadió solución acuosa de carbonato ácido de sodio enfriada con hielo hasta 0 °C y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró, se añadieron 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (28,90 g) obtenido en el Ejemplo 2(2), yoduro de sodio (16,48 g), carbonato de sodio (23,3 g) y N,N-dimetilacetamida (200 mL) al residuo obtenido y la mezcla se agitó a 80 °C durante 18 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El

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residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 50:50, v/v) para dar el compuesto del título (17,88 g, 34%) en forma de un amorfo amarillo.

Ejemplo A68

Ácido 3-{[(4-{[ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico



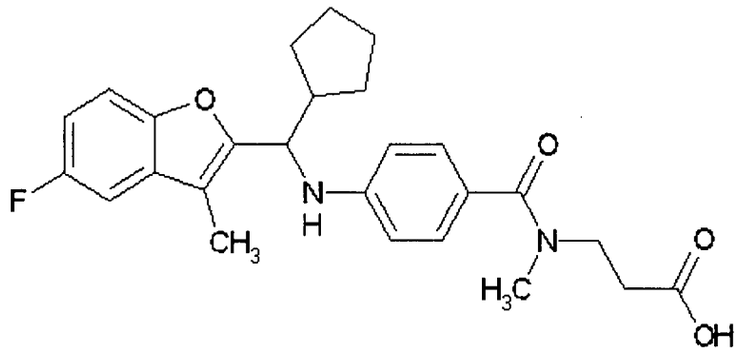

El 3-{[(4-{[ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (460 mg) obtenido en el Ejemplo A67(5) se disolvió en etanol (1,9 mL) y tetrahidrofurano (1,9 mL), una solución acuosa 1 N de hidróxido de sodio (1,9 mL) se añadió y la mezcla se agitó a temperatura ambiente durante 1 h. El solvente se evaporó a presión reducida. Se añadió agua (6 mL) y la mezcla se neutralizó con ácido clorhídrico 1 N bajo enfriamiento con hielo y se agitó durante 1 h. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (352 mg, 81%) en forma de un sólido incoloro.

1302

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,23 - 1,74 (m, 8 H), 1,90 - 2,08 (m, 1 H), 2,24 (s, 3 H), 2,47 (d, J = 8,0 Hz, 1 H), 2,60 - 2,70 (m, 2 H), 3,01 (s, 3 H), 3,69 (t, J = 6,6 Hz, 2 H), 4,36 (d, J = 9,1 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,86 - 6,97 (m, 1 H), 7,07 (dd, J = 8,7, 2,7 Hz, 1 H), 7,18 - 7,31 (m, 3 H).

Ejemplo A69

Ácido 3-{[(4-{[ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




El 3-{[(4-{[ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (4,18 g) obtenido en el Ejemplo A67(5) se disolvió en hexano-etanol (1:1, relación en volumen), se sometió a HPLC usando CHIRALPAK AD (50 mm ID×500 mmL, fabricada por Daicel Chemical Industries, Ltd.) y se eluyó con hexano-etanol (1:1, relación en volumen) como una fase móvil a 30 °C y a una velocidad de flujo de 60 mL/min. La fracción resultante que contenía una forma ópticamente activa con un tiempo de retención más corto se concentró para dar una forma amorfa (2,07 g, 99,9% ee). La forma amorfa obtenida se disolvió en

1303

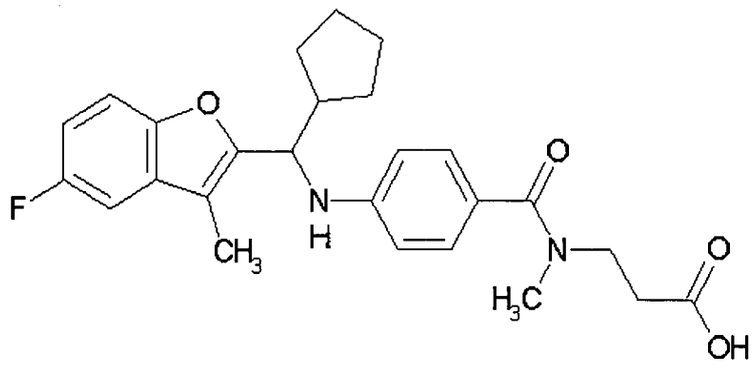
etanol (9 mL) y tetrahidrofurano (9 mL), una solución acuosa 1 N de hidróxido de sodio (8,6 mL) se añadió y la mezcla se agitó a temperatura ambiente durante 30 min. El solvente se evaporó a presión reducida, se añadió agua (15 mL) y la mezcla se neutralizó bajo enfriamiento con hielo con ácido clorhídrico 1 N (8,6 mL) y se agitó durante 1 h. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (1,81 g, 93%, 99,9% ee) como una forma amorfa incolora. El amorfo incoloro obtenido (150 mg) se cristalizó en 2-propanol/agua para dar cristales incoloros que contenían 2-propanol (140 mg). Además, el amorfo incoloro (773 mg) obtenido con anterioridad se cristalizó en etanol/agua para dar cristales con contenido de etanol (756 mg). Los cristales con contenido de etanol (756 mg) se recristalizaron en éter dietílico para dar cristales incoloros (553 mg) libres de solvente.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,15 - 1,72 (m, 7 H), 1,86 - 2,09 (m, 1 H), 2,24 (s, 3 H), 2,40 - 2,53 (m, 1 H), 2,62 (t, J = 6,2 Hz, 2 H), 3,00 (s, 3 H), 3,68 (t, J = 6,6 Hz, 2 H), 4,36 (d, J = 9,0 Hz, 1 H), 6,54 (d, J = 8,7 Hz, 2 H), 6,91 (td, J = 8,9, 2,6 Hz, 1 H), 7,06 (dd, J = 8,7, 2,6 Hz, 1 H), 7,19 - 7,30 (m, 3 H).

Ejemplo A70

Ácido 3-{[(4-{[ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

1304



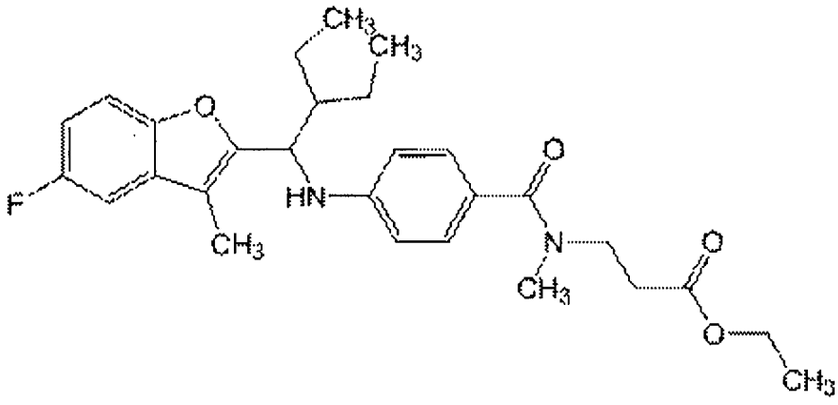

El 3-{[(4-{[ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (4,18 g) obtenido en el Ejemplo A67(5) se disolvió en hexano-etanol (1:1, relación en volumen), se sometió a HPLC usando CHIRALPAK AD (50 mm ID×500 mmL, fabricada por Daicel Chemical Industries, Ltd.) y se eluyó con hexano-etanol (1:1, relación en volumen) como una fase móvil a 30 °C y a una velocidad de flujo 60 mL/min. La fracción resultante que contenía una forma ópticamente activa con un tiempo de retención más largo se concentró para dar una forma amorfa (2,04 g, 99,9% ee). La forma amorfa obtenida (2,04 g) se disolvió en etanol (9 mL) y tetrahidrofurano (9 mL), una solución acuosa 1 N de hidróxido de sodio (8,5 mL) se añadió y la mezcla se agitó a temperatura ambiente durante 30 min. El solvente se evaporó a presión reducida, se añadió agua (15 mL) y la mezcla se neutralizó con ácido clorhídrico 1 N (8,5 mL) bajo enfriamiento con hielo y se agitó durante 1 h. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (1,88 g, 98%, 99,9% ee) como una forma amorfa incolora.

1305

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,23 - 1,75 (m, 7 H), 1,86 - 2,03 (m, 1 H), 2,25 (s, 3 H), 2,39 - 2,54 (m, 1 H), 2,63 (t, J = 6,4 Hz, 2 H), 3,01 (s, 3 H), 3,69 (t, J = 6,6 Hz, 2 H), 4,36 (d, J = 9,1 Hz, 1 H), 4,48 (br. s., 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,92 (td, J = 8,9, 2,7 Hz, 1 H), 7,07 (dd, J = 8,5, 2,5 Hz, 1 H), 7,16 - 7,32 (m, 3 H).

Ejemplo A71

3-{[(4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil](metil)amino}propanoato de etilo



(1) 2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butan-1-ona

A una solución de 5-fluoro-3-metil-1-benzofurano (12,0 g) sintetizada en el Ejemplo A67(2), cloruro de 2-etilbutirilo (9,58 g)in nitrometano (240 mL) se añadió cloruro de aluminio (anhidro) (12,94 g) a 0 °C y la mezcla se agitó durante 1,5 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna

de gel de sílice (hexano-acetato de etilo 100:0 - 90:10, v/v) para dar el compuesto del título (15,02 g, 93%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (t, J = 7,6 Hz, 6 H), 1,59 - 1,67 (m, 2 H), 1,75 - 1,91 (m, 2 H), 2,58 (s, 3 H), 3,26 - 3,42 (m, 1 H), 7,11 - 7,35 (m, 2 H), 7,40 - 7,55 (m, 1 H).

(2) 2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butan-1-ol

2-Etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butan-1-ona (15,0 g) sintetizado con anterioridad se disolvió en un solvente mixto de metanol (50 mL)-tetrahidrofurano (250 mL) y se añadió tetraborohidrato de sodio (90%, 5,1 g) a 0 °C. La mezcla de reacción se agitó a 0 °C durante 1,5 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar el compuesto del título (16,17 g, 100%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,75 - 0,86 (m, 3 H), 0,95 (t, J = 7,6 Hz, 3 H), 1,10 - 1,35 (m, 2 H), 1,66 - 1,94 (m, 3 H), 2,21 (s, 3 H), 4,66 - 4,81 (m, 1 H), 6,90 - 7,02 (m, 1 H), 7,11 (dd, J = 8,7, 2,7 Hz, 1 H), 7,30 - 7,40 (m, 1 H).

(3) 4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butil]amino}benzoato de metilo

A una solución de 2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butan-1-ol (1,00 g) sintetizado con anterioridad en tetrahidrofurano (10 mL) se añadió cloruro de tionilo (320 µL) y la mezcla se agitó a temperatura ambiente durante 3,5 h. La mezcla de reacción se vertió en solución

1307

saturada acuosa de carbonato ácido de sodio helada y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite amarillo (1,11 g). Una solución de este aceite amarillo (1,11 g), 4-aminobenzoato de metilo (638 mg), yoduro de sodio (1,20 g) y carbonato de sodio (852 mg) en N,N-dimetilformamida (10 mL) se agitó a 100 °C durante 20 h. Se añadió agua para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (hexano-acetato de etilo 90:10, v/v) para dar el compuesto del título (790 mg, 52%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 (t, J = 7,5 Hz, 6 H), 1,62 - 1,73 (m, 2 H), 1,84 - 1,94 (m, 2 H), 2,23 (s, 3 H), 3,81 (s, 3 H), 4,46 - 4,52 (m, 1 H), 4,56 - 4,65 (m, 1 H), 4,68 - 4,76 (m, 1 H), 6,54 - 6,61 (m, 2 H), 6,85 - 7,00 (m, 1 H), 7,04 - 7,15 (m, 1 H), 7,29 - 7,37 (m, 1 H), 7,80 (d, J = 9,0 Hz, 2 H).

(4) ácido 4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2il)butil]amino}benzoico

A una mezcla de 4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butil]amino}benzoato de metilo (709 mg) sintetizado con anterioridad, tetrahidrofurano (6 mL) y etanol (6 mL) se añadió solución acuosa 1 N de hidróxido de sodio (3,7 mL) y la mezcla se calentó a reflujo durante 14 h.

1308

Se agregó solución acuosa 1 N de hidróxido de sodio (4,0 mL) y la mezcla luego se agitó con calentamiento a reflujo durante 2 h. Se añadieron solución acuosa 8 N de hidróxido de sodio (2,0 mL) y etanol (2 mL) a la mezcla y la mezcla luego se agitó con calentamiento a reflujo durante 1 h. La mezcla de reacción se concentró a presión reducida, se añadieron solución acuosa 8 N de hidróxido de sodio (4,0 mL), etanol (4 mL) y tetrahidrofurano (4 mL) y la mezcla luego se agitó con calentamiento a reflujo durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, el ácido clorhídrico 1 N se añadió y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 70:30, v/v) para dar el compuesto del título (412 mg, 61%) como una forma amorfa incolora.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,80 - 1,02 (m, 6 H), 1,32 - 1,72 (m, 4 H), 1,83 - 1,97 (m, 1 H), 2,23 (s, 3 H), 4,51 - 4,71 (m, 2 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,87 - 6,98 (m, 1 H), 7,07 (dd, J = 8,3, 2,7 Hz, 1 H), 7,27 - 7,35 (m, 1 H), 7,86 (d, J = 8,7 Hz, 2 H).

(5) 3-{[(4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil](metil)amino}propanoato de etilo

Una mezcla de ácido 4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butil]amino}benzoico (10,77 g) sintetizado con anterioridad, 3-(metilamino)propanoato de etilo (4,59 g),

1309

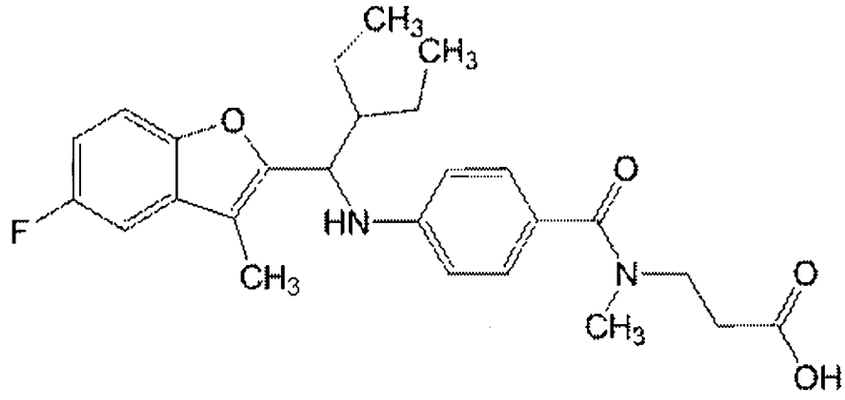
monohidrato de 1-hidroxibenzotriazol (5,34 g), trietilamina (3,53 g), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (6,69 g) y N,N-dimetilformamida (100 mL) se agitó a temperatura ambiente durante 14 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 0:100, v/v) para dar el compuesto del título (9,83 g, 70%) en forma de un amorfo amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,80 - 0,88 (m, 3 H), 0,95 (t, J = 7,3 Hz, 3 H), 1,19 - 1,25 (m, 5 H), 1,33 - 1,54 (m, 2 H), 1,87 (dt, J = 7,3, 4,9 Hz, 1 H), 2,22 (s, 3 H), 2,61 (t, J = 7,0 Hz, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,2 Hz, 2 H), 4,11 (q, J = 6,9 Hz, 2 H), 4,28 (d, J = 8,7 Hz, 1 H), 4,56 (t, J = 8,3 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,92 (td, J = 9,0, 2,6 Hz, 1 H), 7,06 (dd, J = 8,3, 2,6 Hz, 1 H), 7,22 (d, J = 8,7 Hz, 2 H), 7,25 - 7,31 (m, 1 H).

Ejemplo A72

Ácido 3-{[(4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil](metil)amino}propanoico

1310



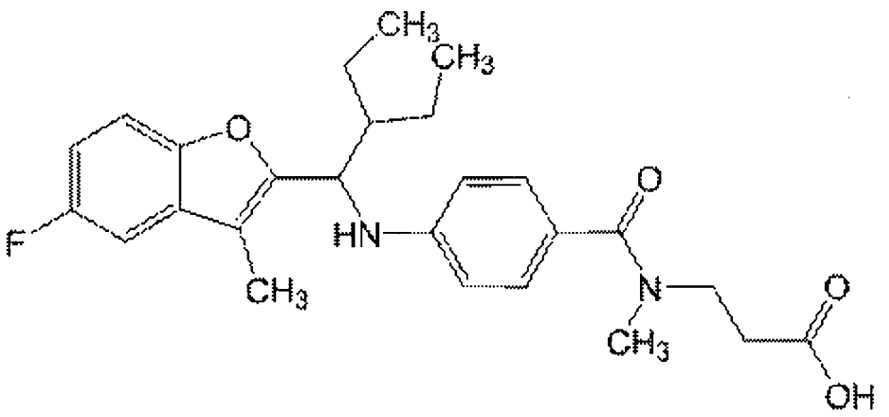
A una mezcla de 3-{[(4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil](metil)amino}propanoato de etilo (132 mg) obtenido en el Ejemplo A71(5) en tetrahidrofurano (1 mL) y etanol (1 mL) se añadió solución acuosa 1 N de hidróxido de sodio (0,54 mL) y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se concentró a presión reducida y el residuo se disolvió en agua (4 mL) y ácido clorhídrico 1 N (0,54 mL) se añadió a 0 °C. La mezcla se agitó a 0 °C durante 1 h y el precipitado resultante se recogió por filtración para dar el compuesto del título (103 mg, 70%) como una forma amorfa incolora.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,79 - 1,01 (m, 6 H), 1,12 - 1,90 (m, 6 H), 2,21 (s, 3 H), 2,58 - 2,69 (m, 2 H), 3,00 (s, 3 H), 3,66 (d, 2 H), 4,56 (d, J = 8,0 Hz, 1 H), 6,55 (d, J = 8,3 Hz, 2 H), 6,92 (td, J = 8,9, 2,7 Hz, 1 H), 7,06 (dd, J = 8,3, 2,7 Hz, 1 H), 7,19 - 7,36 (m, 3 H).

Ejemplo A73

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Ácido 3-{[(4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil](metil)amino}propanoico



El 3-{[(4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil](metil)amino}propanoato de etilo (9,18 g) obtenido en el Ejemplo A71(5) se disolvió en hexano-etanol (1:1, relación en volumen), se sometió a HPLC usando CHIRALPAK AD (50 mm ID×500 mmL, fabricada por Daicel Chemical Industries, Ltd.) y se eluyó con hexano-etanol (1:1, relación en volumen) como una fase móvil a temperatura ambiente y a una velocidad de flujo 60 mL/min. La fracción resultante que contenía una forma ópticamente activa con un tiempo de retención más corto se concentró para dar una forma amorfa (4,56 g, 99,9% ee). La forma amorfa obtenida (4,56 g) se disolvió en etanol (19 mL) y tetrahidrofurano (19 mL), una solución acuosa 1 N de hidróxido de sodio (18,6 mL) se añadió y la mezcla se agitó a temperatura ambiente durante 20 min. El solvente se evaporó a presión reducida. Se añadió agua (30 mL) y la mezcla se neutralizó con ácido clorhídrico 1 N (18,6 mL) bajo enfriamiento con hielo y se agitó durante 20 min. El

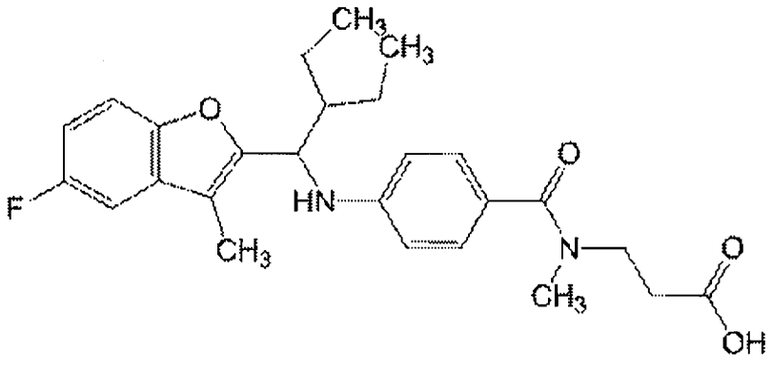
1312

precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (3,63 g, 86%, 99,9% ee) como una forma amorfa incolora. El amorfo incoloro obtenido (1,0 g) se cristalizó en 2-propanol/agua para dar cristales incoloros (927 mg).

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 (t, J = 7,3 Hz, 3 H), 0,94 (t, J = 7,5 Hz, 3 H), 1,11 - 1,72 (m, 4 H), 1,77 - 1,92 (m, 1 H), 2,22 (s, 3 H), 2,65 (t, J = 6,6 Hz, 2 H), 3,02 (s, 3 H), 3,69 (t, J = 6,8 Hz, 2 H), 4,56 (d, J = 7,9 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,92 (td, J = 9,0, 2,6 Hz, 1 H), 7,06 (dd, J = 8,5, 2,4 Hz, 1 H), 7,18 - 7,39 (m, 3 H).

Ejemplo A74

Ácido 3-{[(4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil](metil)amino}propanoico

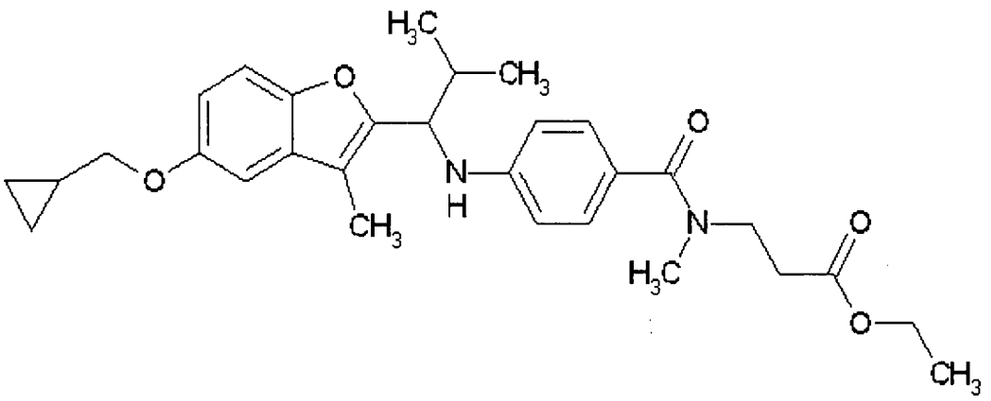



El 3-{[(4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil](metil)amino}propanoato de etilo (9,18 g) obtenido en el Ejemplo A71(5) se disolvió en hexano-etanol (1:1, relación en volumen), se sometió a HPLC usando CHIRALPAK AD (50 mm IDx500 mmL, fabricada por Daicel Chemical Industries, Ltd.) y se eluyó con hexano-etanol (1:1,

relación en volumen) como una fase móvil a temperatura ambiente y a una velocidad de flujo 60 mL/min. La fracción resultante que contenía una forma ópticamente activa con un tiempo de retención más largo se concentró para dar una forma amorfa (4,67 g, 99,9% ee). La forma amorfa obtenida (4,67 g) se disolvió en etanol (20 mL) y tetrahidrofurano (20 mL), solución acuosa 1 N de hidróxido de sodio (19,4 mL) se añadió y la mezcla se agitó a temperatura ambiente durante 20 min. El solvente se evaporó a presión reducida. Se añadió agua (30 mL) y la mezcla se neutralizó con ácido clorhídrico 1 N bajo enfriamiento con hielo y se agitó durante 20 min. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (4,21 g, 96%, 99,9% ee). $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,80 - 0,89 (m, 3 H), 0,94 (t, J = 7,5 Hz, 3 H), 1,16 - 1,71 (m, 4 H), 1,74 - 1,91 (m, 1 H), 2,22 (s, 3 H), 2,62 (t, J = 6,2 Hz, 2 H), 3,01 (s, 3 H), 3,61 - 3,76 (m, 2 H), 4,56 (d, J = 7,9 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,92 (td, J = 9,0, 2,6 Hz, 1 H), 7,06 (dd, J = 8,5, 2,4 Hz, 1 H), 7,16 - 7,31 (m, 3 H).

Ejemplo A75

3-[{[4-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de etilo



(1) 1-bromo-3-metilbutan-2-ona

A una solución de 3-metil-2-butanona (43,0 g) en metanol (300 mL) se añadió gota a gota bromo (80 g) durante 20 min mientras se enfriaba en un baño de hielo. Se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 40 min. Se añadió agua (450 mL) a la mezcla de reacción y la mezcla se agitó durante 20 min. La mezcla de reacción se extrajo dos veces con éter dietílico (500 mL). El extracto se lavó con agua (400 mL), solución acuosa al 10% de carbonato de potasio (400 mL) y salmuera saturada (200 mL), se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto del título (55,9 g) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,17 (d, J = 6,8 Hz, 6 H), 2,88 - 3,05 (m, 1 H), 3,98 (s, 2 H).

(2) 1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ona

Una solución de 2',5'-dihidroxiacetofenona (25,0 g), bromometilciclopropano (24,43 g), carbonato de potasio (27,2 g) en acetonitrilo (400 mL) se agitó con calentamiento a reflujo durante 2,5 h. El bromometilciclopropano (4,4 g) se

añadió a la mezcla y la mezcla luego se agitó con calentamiento a reflujo durante 14 h. La mezcla de reacción se enfrió hasta temperatura ambiente, el material insoluble se filtró y el filtrado se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 10:90, v/v) para dar 1-[5-(ciclopropilmetoxi)-2-hidroxifenil]etanona (35,5 g) en forma de un aceite amarillo con una pureza del 70%. Una solución de la 1-[5-(ciclopropilmetoxi)-2-hidroxifenil]etanona obtenida (35,5 g), 1-bromo-3-metilbutan-2-ona (35,5 g) sintetizada con anterioridad y carbonato de potasio (66,3 g) en N,N-dimetilformamida (350 mL) se agitó a temperatura ambiente durante 1 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. 1,8-Diazabiciclo[5,4,0]undec-7-eno (22,5 mL) y N,N-dimetilformamida (300 mL) se añadieron al residuo obtenido y la mezcla se agitó a 100 °C durante 30 min. La mezcla de reacción se enfrió hasta temperatura ambiente, se añadió ácido clorhídrico 1 N (300 mL) y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 90:10, v/v) para dar el compuesto del título (19,91 g, 45%) en forma de un sólido incoloro.

1316

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,29 - 0,50 (m, 2 H), 0,61 - 0,73 (m, 2 H), 1,01 - 1,46 (m, 7 H), 2,57 (s, 3 H), 3,44 - 3,68 (m, 1 H), 3,86 (d, J = 7,2 Hz, 2 H), 7,00 (d, J = 2,3 Hz, 1 H), 7,11 (dd, J = 9,0, 2,6 Hz, 1 H), 7,39 (d, J = 9,0 Hz, 1 H).

(3) 1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ol

1-[5-(Ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ona (19,91 g) sintetizada con anterioridad se disolvió en un solvente mixto de metanol (40 mL)-tetrahidrofurano (200 mL) y tetraborohidrato de sodio (90%, 5,53 g) se añadió a 0 °C. La mezcla de reacción se agitó a 0 °C durante 30 min. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar el compuesto del título (22,74 g, 100%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,32 - 0,42 (m, 2 H), 0,60 - 0,71 (m, 2 H), 0,81 (d, 3 H), 1,12 (d, J = 6,4 Hz, 3 H), 1,26 - 1,36 (m, 1 H), 1,99 (d, J = 6,0 Hz, 1 H), 2,17 - 2,28 (m, 4 H), 3,84 (d, 2 H), 4,45 (dd, J = 8,3, 6,4 Hz, 1 H), 6,84 - 6,96 (m, 2 H), 7,29 (d, J = 8,7 Hz, 1 H).

(4) 3-[{[4-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

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A una solución de 1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ol (22,74 g) obtenida con anterioridad en tetrahidrofurano (200 mL) se añadió cloruro de tionilo (6,4 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 1,5 h. A la mezcla de reacción helada de 0 °C se añadió solución acuosa de carbonato ácido de sodio y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró, se añadieron 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (19,2 g) obtenido en el Ejemplo 2(2), yoduro de sodio (21,9 g), carbonato de sodio (15,4 g) y N,N-dimetilacetamida (200 mL) al residuo obtenido y la mezcla se agitó a 80 °C durante 1,5 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 50:50, v/v) para dar el compuesto del título (18,34 g, 50%) en forma de un amorfo amarillo.

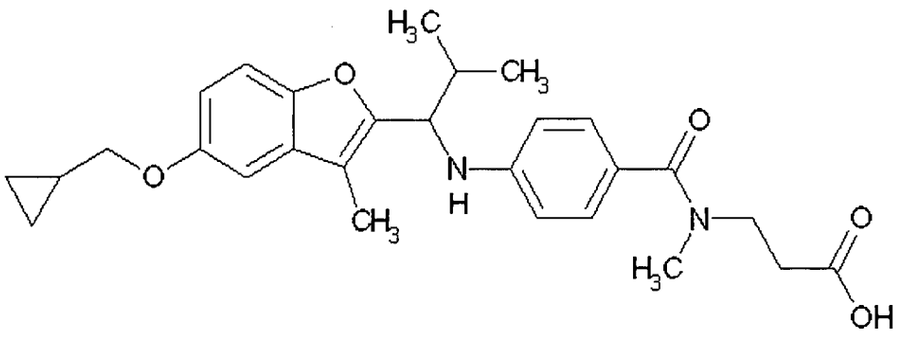
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,29 - 0,40 (m, 2 H), 0,58 - 0,70 (m, 2 H), 0,91 (d, J = 6,8 Hz, 3 H), 1,12 (d, J = 6,8 Hz, 3 H), 1,19 - 1,33 (m, 4 H), 2,17 - 2,28 (m, 4 H), 2,61 (t, J = 6,8 Hz, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,2 Hz, 2 H), 3,82 (d, J = 7,2 Hz, 2 H), 4,05 - 4,16 (m, 2 H), 4,27 -

1318

4,38 (m, 2 H), 6,57 (d, J = 9,0 Hz, 2 H), 6,78 - 6,91 (m, 2 H), 7,17 - 7,25 (m, 3 H).

Ejemplo A76

Ácido 3-[{[4-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico



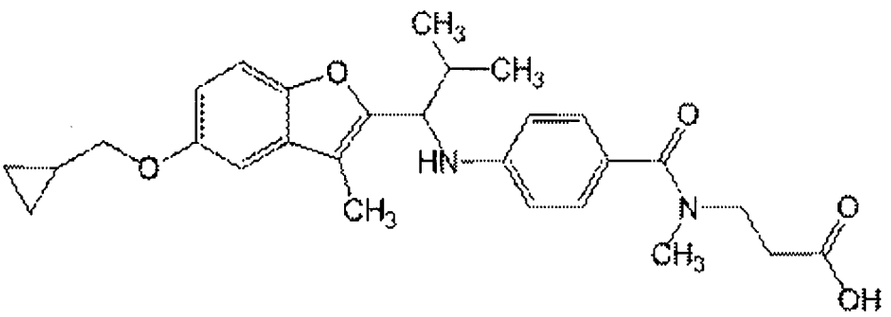
A una mezcla de 3-[{[4-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (667 mg) obtenido en el Ejemplo A75(4) en tetrahidrofurano (3 mL) y etanol (3 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,6 mL) y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se concentró a presión reducida, el residuo se disolvió en agua (4 mL) y ácido clorhídrico 1 N (2,6 mL) se añadió a 0 °C. La mezcla se agitó a 0 °C durante 30 min y el precipitado resultante se recogió por filtración para dar el compuesto del título (509 mg, 81%) como una forma amorfa incolora.

1319

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,28 - 0,40 (m, 2 H), 0,58 - 0,71 (m, 2 H), 0,91 (d, J = 6,8 Hz, 3 H), 1,11 (d, J = 6,8 Hz, 3 H), 1,23 - 1,34 (m, 1 H), 2,17 - 2,28 (m, 4 H), 2,64 (t, J = 6,4 Hz, 2 H), 3,02 (s, 3 H), 3,69 (t, J = 6,4 Hz, 2 H), 3,82 (d, J = 7,2 Hz, 2 H), 4,31 (d, J = 8,0 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,78 - 6,91 (m, 2 H), 7,19 - 7,25 (m, 3 H).

Ejemplo A77

Ácido 3-[{[4-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico




El 3-[{[4-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (18,23 g) obtenido en el Ejemplo A75(4) se disolvió en hexano-etanol (1:1, relación en volumen), se sometió a HPLC usando CHIRALPAK AD (50 mm IDx500 mmL, fabricada por Daicel Chemical Industries, Ltd.) y se eluyó con hexano-etanol (1:1 - 1:4, relación en volumen) como una fase móvil a temperatura ambiente y a una velocidad de flujo 60 - 50 mL/min. La fracción resultante que contenía una forma ópticamente activa con un tiempo de retención más corto se concentró para dar

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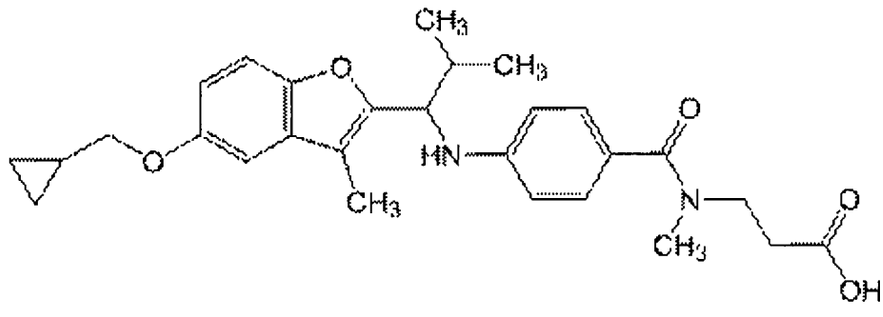
una forma amorfa (9,08 g, 99,9% ee). La forma amorfa obtenida (4,72 g) se disolvió en etanol (19 mL) y tetrahidrofurano (19 mL), una solución acuosa 1 N de hidróxido de sodio (18,6 mL) se añadió y la mezcla se agitó a temperatura ambiente durante 20 min. El solvente se evaporó a presión reducida. Se añadió agua (40 mL) y la mezcla se neutralizó con ácido clorhídrico 1 N (18,6 mL) bajo enfriamiento con hielo y se agitó durante 20 min. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (4,27 g, 96%, 99,9% ee) como una forma amorfa incolora.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,31 - 0,38 (m, 2 H), 0,58 - 0,68 (m, 2 H), 0,90 (d, J = 6,8 Hz, 3 H), 1,12 (d, J = 6,4 Hz, 3 H), 1,28 (s, 1 H), 2,17 - 2,29 (m, 4 H), 2,63 (t, J = 6,4 Hz, 2 H), 3,01 (s, 3 H), 3,69 (t, J = 6,4 Hz, 2 H), 3,82 (d, J = 6,8 Hz, 2 H), 4,31 (d, J = 7,5 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,78 - 6,89 (m, 2 H), 7,19 - 7,27 (m, 3 H).

Ejemplo A78

Ácido 3-[{[4-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-

metilpropil}amino)fenil]carbonil}(metil)amino]propanoico



El 3-[{[4-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (18,23 g) obtenido en el Ejemplo A75(4) se disolvió en hexano-etanol (1:1, relación en volumen), se sometió a HPLC usando CHIRALPAK AD (50 mm IDx500 mmL, fabricada por Daicel Chemical Industries, Ltd.) y se eluyó con hexano-etanol (1:1 - 1:4, relación en volumen) como una fase móvil a temperatura ambiente y a una velocidad de flujo 60 - 50 mL/min. La fracción resultante que contenía una forma ópticamente activa con un tiempo de retención más largo se concentró para dar una forma amorfa (9,08 g, 99,9% ee). La forma amorfa obtenida (4,73 g) se disolvió en etanol (19 mL) y tetrahidrofurano (19 mL), una solución acuosa 1 N de hidróxido de sodio (18,7 mL) se añadió y la mezcla se agitó a temperatura ambiente durante 20 min. El solvente se evaporó a presión reducida. Se añadió agua (40 mL) y la mezcla se neutralizó con ácido clorhídrico 1 N (18,7 mL) bajo enfriamiento con hielo y se agitó durante 30 min. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (4,02 g, 90%, 98,8% ee) como una forma amorfa incolora. El amorfo incoloro obtenido (500 mg) se disolvió en acetato de etilo y la mezcla se lavó con agua y salmuera saturada. La capa orgánica se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar un amorfo incoloro. El amorfo incoloro obtenido se cristalizó en acetato de etilo/hexano para dar cristales incoloros (401 mg). Además, un producto amorfo (60 mg) obtenido por división se

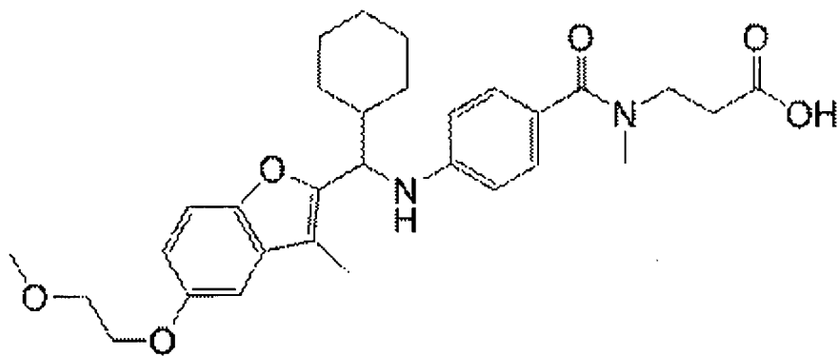
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cristalizó en éter dietílico/hexano para dar cristales incoloros (45 mg).

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,27 - 0,42 (m, 2 H), 0,56 - 0,66 (m, 2 H), 0,91 (d, J = 6,8 Hz, 3 H), 1,12 (d, J = 6,8 Hz, 3 H), 1,28 (s, 1 H), 2,18 - 2,28 (m, 4 H), 2,66 (t, J = 6,4 Hz, 2 H), 3,03 (s, 3 H), 3,70 (t, J = 6,6 Hz, 2 H), 3,82 (d, J = 7,2 Hz, 2 H), 4,31 (d, J = 7,5 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,73 - 6,89 (m, 2 H), 7,19 - 7,25 (m, 3 H).

Ejemplo A79

Ácido 3-[{[4-({ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico




(1) 1-[2-hidroxi-5-(2-metoxietoxi)fenil]etanona

A una solución (250 mL) de 1-(2,5-dihidroxifenil)etanona (11,0 g) en acetonitrilo se añadieron bromuro de 2-metoxietilo (19,6 mL) y carbonato de potasio (12,0 g) a temperatura ambiente y la mezcla se calentó a reflujo durante 15 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y se filtró a través de celite y el filtrado se

concentró a presión reducida. Se añadió solución acuosa saturada de cloruro de amonio al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:10, relación en volumen) para dar el compuesto objeto del título (7,6 g, 50%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,61 (s, 3 H), 3,46 (s, 3 H), 3,66 - 4,21 (m, 4 H), 6,92 (d, J = 9,0 Hz, 1 H), 7,15 (d, J = 9,0 Hz, 1 H), 7,22 - 7,26 (m, 1 H), 11,84 (s, 1 H).

(2) ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metanona

1-[2-Hidroxi-5-(2-metoxietoxi)fenil]etanona (7,0 g) sintetizada en el punto (1) antes mencionado se disolvió en N,N-dimetilformamida (140 mL). Se añadieron carbonato de potasio (13,8 g) y 2-bromo-1-ciclohexiletanona (8,9 g) sintetizada en el Ejemplo A51(1) a la mezcla de reacción a temperatura ambiente y la mezcla se agitó durante 15 h. La mezcla de reacción se filtró a través de celite, se añadió agua (200 mL) y la mezcla se extrajo con éter dietílico (100 mLx2). El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en solución de N,N-dimetilformamida (100 mL), se añadió DBU (5,3 mL) a temperatura ambiente y la mezcla se agitó a 100 °C durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, el ácido

clorhídrico 1 N (100 mL) se añadió y la mezcla se extrajo con éter dietílico (100 mL×2). El extracto se lavó con agua, solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:20, relación en volumen) para dar el compuesto objeto del título (10,3 g, 98%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,32 - 2,00 (m, 11 H), 2,56 (s, 3 H), 3,30 (d, J = 3,4 Hz, 1 H), 3,48 (s, 3 H), 3,75 - 3,85 (m, 2 H), 4,15 - 4,25 (m, 2 H), 7,04 (d, J = 2,5 Hz, 1 H), 7,13 (dd, J = 8,9, 2,5 Hz, 1 H), 7,40 (d, J = 8,9 Hz, 1 H).

(3) ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metanol

Ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metanona (10,3 g) sintetizada en el punto (2) antes mencionado se disolvió en un solvente mixto de tetrahidrofurano (180 mL) y metanol (20 mL). La mezcla de reacción se enfrió con hielo y se añadió borohidruro de sodio (90%, 2,7 g) y la mezcla de reacción se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se enfrió con hielo nuevamente, se añadieron cuidadosamente agua (10 mL) y ácido clorhídrico 1 N (100 mL) y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un producto crudo (10,3 g) del compuesto objeto del título en forma de un aceite amarillo pálido.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,15 - 2,02 (m, 11 H), 2,56 (s, 3 H), 3,48 (s, 3 H), 3,73 - 3,87 (m, 2 H), 4,14 - 4,26 (m, 2 H), 4,44 -4,46 (m, 1 H), 7,04 (d, J = 2,6 Hz, 1 H), 7,13 (dd, J = 9,0, 2,6 Hz, 1 H), 7,40 (d, J = 9,0 Hz, 1 H).

(4) 3-[{[4-({ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

A una solución (200 mL) de ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metanol (10,3 g) sintetizada en el punto (3) antes mencionado en tetrahidrofurano se añadió cloruro de tionilo (4,7 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min y se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (100 mL) se añadió cuidadosamente. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (150 mL), se añadieron yoduro de sodio (8,0 g), carbonato de sodio (5,3 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (8,9 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar

el compuesto objeto del título (8,5 g, 43%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 2,14 (m, 14 H), 2,21 (s, 3 H), 2,61 (t, J = 6,8 Hz, 2 H), 3,01 (s, 3 H), 3,46 (s, 3 H), 3,60 - 3,81 (m, 4 H), 4,01 - 4,21 (m, 4 H), 4,27 - 4,46 (m, 2 H), 6,56 (d, J = 8,3 Hz, 2 H), 6,76 - 6,95 (m, 2 H), 7,14 - 7,25 (m, 3 H).

(5) ácido 3-[{[4-({ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

El 3-[{[4-({ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (5,4 g) sintetizado en el punto (4) antes mencionado se disolvió en etanol (150 mL), una solución acuosa 1 N de hidróxido de sodio (15 mL) se añadió a temperatura ambiente y la mezcla se agitó a 50 °C durante 0,5 h. El etanol se evaporó a presión reducida, el ácido clorhídrico 1 N (20 mL) se añadió al residuo y la mezcla se extrajo con éter dietílico. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (3,0 g, 59%) en forma de un sólido blanco.

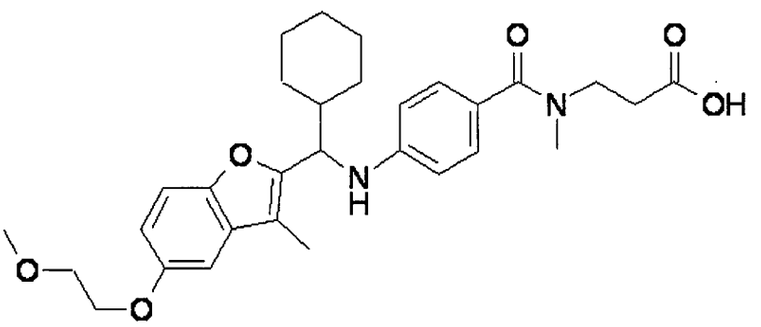
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 2,14 (m, 12 H), 2,21 (s, 3 H), 2,66 (t, J = 6,1 Hz, 2 H), 3,03 (s, 3 H), 3,46 (s, 3 H), 3,60 - 3,81 (m, 4 H), 4,01 - 4,21 (m, 4 H), 4,35 (d, J =

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7,8 Hz, 2 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,76 - 6,95 (m, 2 H), 7,14 - 7,25 (m, 3 H).

Ejemplo A80

Ácido 3-[{[4-({ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



Ácido 3-[{[4-({ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

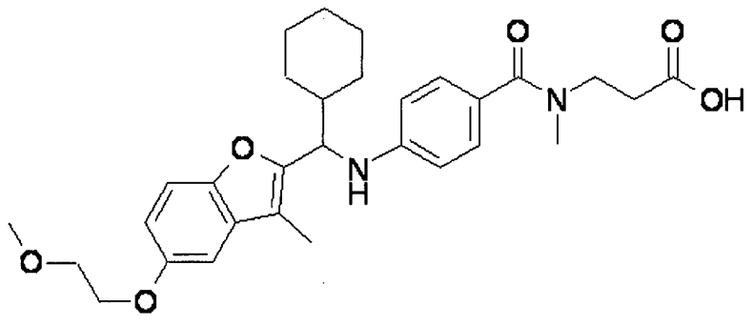
El ácido 3-[{[4-({Ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico (3,0 g) sintetizado en el Ejemplo A79(5) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (5mm i.d.×500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/2-propanol/ácido trifluoroacético (500/500/1), velocidad de flujo: 60 mL/min, temperatura de la columna: 30 °C). A la fracción que contenía una forma ópticamente activa con un tiempo de retención más corto en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se añadió

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trietilamina (10 mL) y la mezcla se concentró para dar una sal de trietilamina (3,7 g) del compuesto objeto del título. Se añadió ácido clorhídrico 1 N (30 mL) y la mezcla se extrajo con éter dietílico. El extracto se lavó con agua y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (1,49 g, 99,9% ee) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 2,14 (m, 12 H), 2,21 (s, 3 H), 2,66 (t, J = 6,1 Hz, 2 H), 3,03 (s, 3 H), 3,46 (s, 3 H), 3,60 - 3,81 (m, 4 H), 4,01 - 4,21 (m, 4 H), 4,35 (d, J = 7,8 Hz, 2 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,76 - 6,95 (m, 2 H), 7,14 - 7,25 (m, 3 H).

Ejemplo A81

Ácido 3-[{[4-({ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



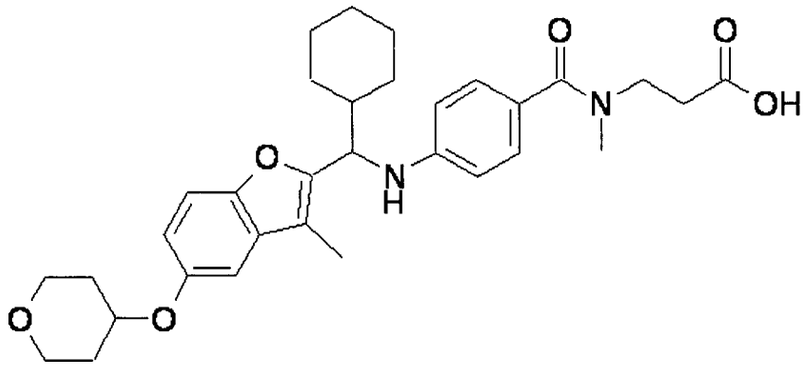

(1) Ácido 3-[{[4-({ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

El ácido 3-[{[4-({Ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico (3,0 g) sintetizado en el Ejemplo A79(5) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50mm i.d.x500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/2-propanol/trifluoroacético (500/500/1), velocidad de flujo: 60 mL/min, temperatura de la columna: 30 °C). A la fracción que contenía una forma ópticamente activa con un tiempo de retención más largo en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se añadió trietilamina (30 mL) y la mezcla se concentró para dar una sal de trietilamina (9,2 g) del compuesto objeto del título. Se añadió ácido clorhídrico 1 N (30 mL) y la mezcla se extrajo con éter dietílico. El extracto se lavó con agua y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (1,50 g, 99,9% ee) en forma de un sólido blanco.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 2,14 (m, 12 H), 2,21 (s, 3 H), 2,66 (t, J = 6,1 Hz, 2 H), 3,03 (s, 3 H), 3,46 (s, 3 H), 3,60 - 3,81 (m, 4 H), 4,01 - 4,21 (m, 4 H), 4,35 (d, J = 7,8 Hz, 2 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,76 - 6,95 (m, 2 H), 7,14 - 7,25 (m, 3 H).

Ejemplo A82

Ácido 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

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(1) 1-[5-(benciloxi)-2-hidroxifenil]etanona

A una solución (400 mL) de 1-(2,5-dihidroxifenil)etanona (25,0 g) en acetonitrilo se añadieron bromuro de bencilo (19,6 mL) y carbonato de potasio (25,0 g) a temperatura ambiente y la mezcla se calentó a reflujo durante 2 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, se filtró a través de celite y el filtrado se concentró a presión reducida. Se añadió solución acuosa saturada de cloruro de amonio al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido. El sólido obtenido se lavó con etanol-éter isopropílico para dar el compuesto objeto del título (31,0 g, 80%) en forma de un sólido verde amarillento.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,58 (s, 3 H), 5,05 (s, 2 H), 7,11 - 7,53 (m, 8 H), 11,85 (s, 1 H).

(2) [5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metanona

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A una solución (500 mL) de 1-[5-(benciloxi)-2-hidroxifenil]etanona (29,5 g) sintetizada en el punto (1) antes mencionado en N,N-dimetilformamida se añadieron carbonato de potasio (41,4 g) y 2-bromo-1-ciclohexiletanona (25,0 g) sintetizada en el Ejemplo A51(1) a temperatura ambiente y la mezcla se agitó a 60 °C durante 15 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, se filtró a través de celite. Se añadió agua al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido. El sólido obtenido se lavó con etanol-éter isopropílico para dar el compuesto objeto del título (18,0 g, 43%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,17 - 2,10 (m, 10 H), 2,56 (s, 3 H), 3,17 - 3,43 (m, 1 H), 5,12 (s, 2 H), 7,04 - 7,21 (m, 2 H), 7,30 - 7,51 (m, 6 H).

(3) ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metanona

La [5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metanona (7,3 g) sintetizada en el punto (2) antes mencionado se disolvió en etanol (150 mL) y tetrahidrofurano (30 mL) y se añadió complejo de carbono de paladio-etilendiamina (1,0 g) a temperatura ambiente. La mezcla de reacción se agitó a 60 °C durante 3 h bajo una atmósfera de hidrógeno (1 atm), se dejó enfriar hasta temperatura ambiente y el catalizador se filtró. El filtrado se concentró a presión reducida para dar un producto crudo

(5,2 g, cuantitativo) del compuesto objeto del título en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,21 - 2,03 (m, 10 H), 2,54 (s, 3 H), 3,22 - 3,38 (m, 1 H), 4,78 (br. s., 1 H), 6,96 - 7,05 (m, 2 H), 7,38 (d, J = 9,5 Hz, 1 H).

(4) ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metanona

Ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metanona (5,2 g) sintetizada en el punto (3) antes mencionado se disolvió en dimetilformamida (100 mL) y fostato de potasio (7,4 g) y 4-metilbencensulfonato de tetrahidro-2H-piran-4-ilo (9,0 g) sintetizado por el método del documento EP-A-1367058 se añadieron a la mezcla a temperatura ambiente y la mezcla se agitó a 80 °C durante la noche. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, se añadió agua (150 mL) y la mezcla se extrajo con éter dietílico (100 mL×2). El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:10, relación en volumen) para dar el compuesto objeto del título (7,1 g, 99%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,35 - 2,10 (m, 14 H), 2,56 (s, 3 H), 3,24 - 3,38 (m, 1 H), 3,50 - 3,65 (m, 2 H), 3,95 - 4,07 (m, 2 H), 4,50 (tt, J = 7,8, 3,9 Hz, 1 H), 7,04 - 7,16 (m, 2 H), 7,42 (d, J = 8,7 Hz, 1 H).

(5) ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metanol

Ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metanona (7,1 g) sintetizada en el punto (4) antes mencionado se disolvió en tetrahidrofurano (200 mL) y metanol (20 mL) y se añadió borohidruro de sodio (90%, 1,6 g) bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se enfrió con hielo nuevamente, agua (10 mL) y ácido clorhídrico 1 N (100 mL) se añadieron cuidadosamente y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un producto crudo (6,7 g, 98%) del compuesto objeto del título en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,82 - 2,14 (m, 15 H), 2,18 (s, 3 H), 3,57 (ddd, J = 11,6, 8,4, 3,4 Hz, 2 H), 3,93 - 4,06 (m, 2 H), 4,36 - 4,59 (m, 2 H), 6,89 (dd, J = 8,7, 2,3 Hz, 1 H), 6,97 (d, J = 2,3 Hz, 1 H), 7,31 (d, J = 8,7 Hz, 1 H).

(6) 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

Ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metanol (6,7 g) sintetizado en el punto (5) antes mencionado se disolvió en tetrahidrofurano (120 mL) y el cloruro de tionilo (2,6 mL) se añadió a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de hidrógeno-carbonato de sodio (100

mL) se añadió cuidadosamente. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (100 mL), se añadieron yoduro de sodio (5,3 g), carbonato de sodio (3,5 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (4,9 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (6,1 g, 54%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 2,10 (m, 18 H), 2,21 (s, 3 H), 2,61 (t, J = 7,0 Hz, 2 H), 3,01 (s, 3 H), 3,55 (ddd, J = 11,7, 8,5, 3,2 Hz, 2 H), 3,70 (t, J = 7,0 Hz, 2 H), 3,90 - 4,05 (m, 2 H), 4,27 - 4,52 (m, 4 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,77 - 6,96 (m, 2 H), 7,15 - 7,25 (m, 3 H).

(7) ácido 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

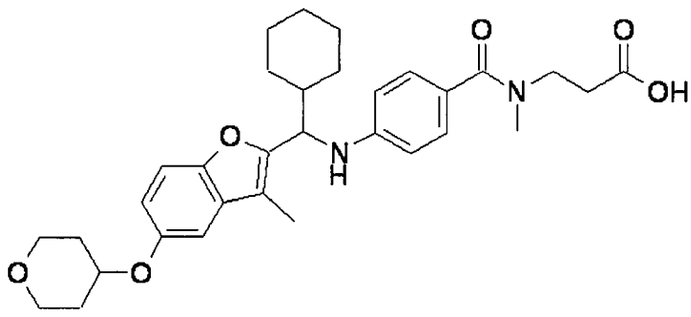
3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,6 g) sintetizado en el punto (6) antes mencionado se disolvió en etanol (20 mL), se añadió solución acuosa 1 N de

hidróxido de sodio (3 mL) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 12 h. El etanol se evaporó a presión reducida, el ácido clorhídrico 1 N (3 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se recristalizó en acetona para dar el compuesto objeto del título (0,5 g, 77%) en forma de cristales incoloros.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 - 2,14 (m, 15 H), 2,21 (s, 3 H), 2,67 (t, J = 6,2 Hz, 2 H), 3,03 (s, 3 H), 3,56 (ddd, J = 11,6, 8,4, 3,0 Hz, 2 H), 3,69 (t, J = 6,6 Hz, 2 H), 3,88 - 4,08 (m, 2 H), 4,27 - 4,53 (m, 2 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,78 - 6,99 (m, 2 H), 7,17 - 7,26 (m, 3 H).

Ejemplo A83

Ácido 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico




(1) 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-

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il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

El 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (4,0 g) sintetizado en el Ejemplo A82(6) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50mm i.d.x500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (200/800), velocidad de flujo: 60 mL/min, temperatura de la columna: 30 °C). La fracción que contenía una forma ópticamente activa con un tiempo de retención más corto en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar el compuesto objeto del título (1,8 g, 99,9% ee).

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 2,10 (m, 18 H), 2,21 (s, 3 H), 2,61 (t, J = 7,0 Hz, 2 H), 3,01 (s, 3 H), 3,55 (ddd, J = 11,7, 8,5, 3,2 Hz, 2 H), 3,70 (t, J = 7,0 Hz, 2 H), 3,90 - 4,05 (m, 2 H), 4,27 - 4,52 (m, 4 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,77 - 6,96 (m, 2 H), 7,15 - 7,25 (m, 3 H).

(2) ácido 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

El 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (1,8 g) ópticamente resuelto en el punto (1) antes mencionado se disolvió en etanol (20 mL), una solución acuosa

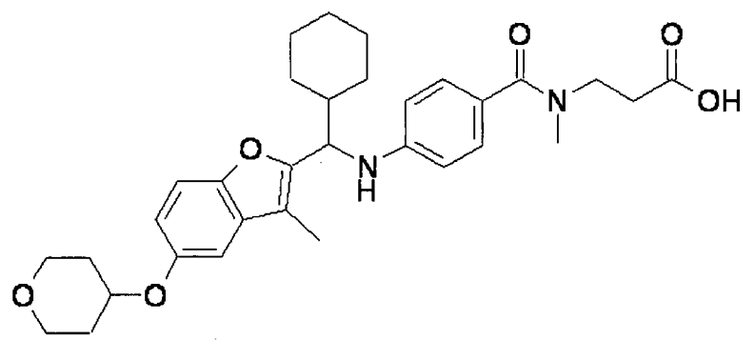
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1 N de hidróxido de sodio (5 mL) se añadió a temperatura ambiente y la mezcla se agitó a 50 °C durante 0,5 h. El etanol se evaporó a presión reducida, el ácido clorhídrico 1 N (5 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se recristalizó en acetona para dar el compuesto objeto del título (1,6 g, 95%, 99,9% ee) en forma de cristales incoloros.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 - 2,14 (m, 15 H), 2,21 (s, 3 H), 2,67 (t, J = 6,2 Hz, 2 H), 3,03 (s, 3 H), 3,56 (ddd, J = 11,6, 8,4, 3,0 Hz, 2 H), 3,69 (t, J = 6,6 Hz, 2 H), 3,88 - 4,08 (m, 2 H), 4,27 - 4,53 (m, 2 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,78 - 6,99 (m, 2 H), 7,17 - 7,26 (m, 3 H).

Ejemplo A84

Ácido 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



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(1) 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

El 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (4,0 g) sintetizado en el Ejemplo A82(6) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50mm i.d.×500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (200/800), velocidad de flujo: 60 mL/min, temperatura de la columna: 30 °C). La fracción que contenía una forma ópticamente activa con un tiempo de retención más largo en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar el compuesto objeto del título (1,8 g, 99,9% ee).

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 2,10 (m, 18 H), 2,21 (s, 3 H), 2,61 (t, J = 7,0 Hz, 2 H), 3,01 (s, 3 H), 3,55 (ddd, J = 11,7, 8,5, 3,2 Hz, 2 H), 3,70 (t, J = 7,0 Hz, 2 H), 3,90 - 4,05 (m, 2 H), 4,27 - 4,52 (m, 4 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,77 - 6,96 (m, 2 H), 7,15 - 7,25 (m, 3 H).

(2) ácido 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

El 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de

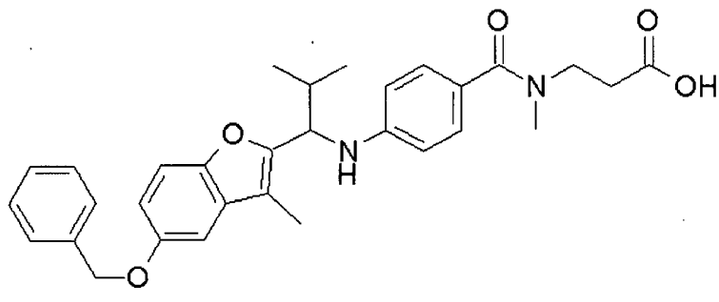
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etilo (1,8 g) ópticamente resuelto en el punto (1) antes mencionado se disolvió en etanol (20 mL), solución acuosa 1 N de hidróxido de sodio (5 mL) se añadió a temperatura ambiente y la mezcla se agitó a 50 °C durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (5 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se recristalizó en acetona para dar el compuesto objeto del título (1,5 g, 88%, 99,9% ee) en forma de cristales incoloros.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 - 2,14 (m, 15 H), 2,21 (s, 3 H), 2,67 (t, J = 6,2 Hz, 2 H), 3,03 (s, 3 H), 3,56 (ddd, J = 11,6, 8,4, 3,0 Hz, 2 H), 3,69 (t, J = 6,6 Hz, 2 H), 3,88 - 4,08 (m, 2 H), 4,27 - 4,53 (m, 2 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,78 - 6,99 (m, 2 H), 7,17 - 7,26 (m, 3 H).

Ejemplo A85

Ácido 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico



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(1)1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ona

A una solución (200 mL) de 1-[5-(benciloxi)-2-hidroxifenil]etanona (16,1 g) sintetizada en el Ejemplo A82(1) en N,N-dimetilformamida se añadieron a temperatura ambiente carbonato de potasio (27,6 g) y 1-bromo-3-metilbutan-2-ona (14,3 g) sintetizada en el Ejemplo A75(1) y la mezcla se agitó durante 15 h. La mezcla de reacción se filtró a través de celite, se añadió agua (200 mL) y la mezcla se extrajo con éter dietílico (100 mL×2). El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilformamida (100 mL) y se añadió DBU (9,9 mL) a temperatura ambiente. La mezcla de reacción se agitó a 100 °C durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, el ácido clorhídrico 1 N (150 mL) se añadió y la mezcla se extrajo con éter dietílico (100 mL×2). El extracto se lavó con agua, solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se recristalizó en etanol-éter diisopropílico para dar el compuesto objeto del título (11,7 g, 57%) en forma de cristales de color amarillo pálido.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,23 (d, J = 6,8 Hz, 6 H), 2,57 (s, 3 H), 3,57 (dt, J = 13,8, 6,8 Hz, 1 H), 5,12 (s, 2 H), 7,11 (d, J = 2,6 Hz, 1 H), 7,13 - 7,21 (m, 1 H), 7,30 - 7,55 (m, 6 H).

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(2) 1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ol

1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ona (11,7 g) sintetizada en el punto (1) antes mencionado se disolvió en a tetrahidrofurano (150 mL) y metanol (15 mL) y se añadió borohidruro de sodio (90%, 3,0 g) bajo enfriamiento con hielo. Se retiró el baño de hielo, la mezcla de reacción se agitó a temperatura ambiente durante 2 h. La mezcla se enfrió con hielo nuevamente, agua (10 mL) y ácido clorhídrico 1 N (100 mL) se añadieron cuidadosamente y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (11,3 g, cuantitativo) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,82 (d, J = 6,8 Hz, 3 H), 1,12 (d, J = 6,8 Hz, 3 H), 1,55 (d, J = 2,6 Hz, 1 H), 2,11 - 2,34 (m, 4 H), 4,46 (dd, J = 8,3, 6,0 Hz, 1 H), 5,10 (s, 2 H), 6,82 - 7,08 (m, 2 H), 7,28 - 7,55 (m, 6 H).

(3) 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

El 1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ol (10,2 g) sintetizado en el punto (2) antes mencionado se disolvió en tetrahidrofurano (150 mL) y cloruro de tionilo (4,3 mL) se añadió a temperatura ambiente. La

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mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y solución saturada acuosa de carbonato ácido de sodio (100 mL) se añadió cuidadosamente. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (200 mL), se añadieron yoduro de sodio (7,4 g), carbonato de sodio (5,0 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (8,2 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (6,3 g, 35%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,8 Hz, 3 H), 1,12 (d, J = 6,8 Hz, 3 H), 1,23 (t, J = 7,2 Hz, 3 H), 2,13 - 2,33 (m, 4 H), 2,61 (t, J = 7,2 Hz, 2 H), 3,01 (s, 3 H), 3,71 (t, J = 7,2 Hz, 2 H), 4,12 (q, J = 7,2 Hz, 2 H), 4,25 - 4,46 (m, 2 H), 5,09 (s, 2 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,81 - 7,02 (m, 2 H), 7,15 - 7,25 (m, 3 H), 7,30 - 7,59 (m, 5 H).

(4) ácido 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico

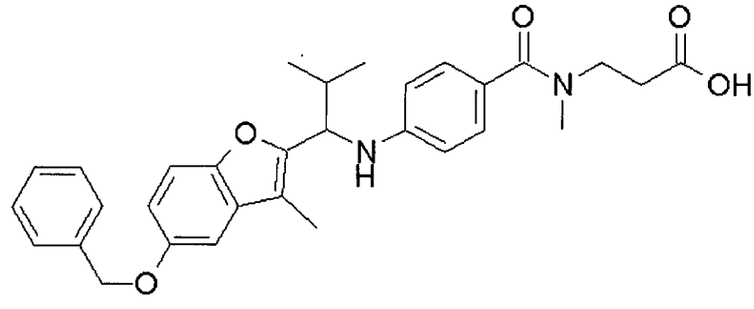
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El 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,38 g) sintetizado en el punto (3) antes mencionado se disolvió en etanol (5 mL), una solución acuosa 1 N de hidróxido de sodio (1,5 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida, el ácido clorhídrico 1 N (1,5 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (0,28 g, 79%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,8 Hz, 3 H), 1,12 (d, J = 6,8 Hz, 3 H), 2,18 - 2,30 (m, 4 H), 2,66 (t, J = 6,2 Hz, 2 H), 3,03 (s, 3 H), 3,69 (t, J = 6,2 Hz, 2 H), 4,32 (d, J = 7,5 Hz, 1 H), 5,08 (s, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,83 - 7,02 (m, 2 H), 7,17 - 7,26 (m, 3 H), 7,30 - 7,53 (m, 5 H).

Ejemplo A86

Ácido 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico



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(1) 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

El 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (3,0 g) sintetizado en el Ejemplo A85(3) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50mm i.d.×500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (200/800), velocidad de flujo: 60 mL/min, temperatura de la columna: 30 °C). La fracción que contenía una forma ópticamente activa con un tiempo de retención más largo en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar el compuesto objeto del título (1,23 g, 99,9% ee).

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,8 Hz, 3 H), 1,12 (d, J = 6,8 Hz, 3 H), 1,23 (t, J = 7,2 Hz, 3 H), 2,13 - 2,33 (m, 4 H), 2,61 (t, J = 7,2 Hz, 2 H), 3,01 (s, 3 H), 3,71 (t, J = 7,2 Hz, 2 H), 4,12 (q, J = 7,2 Hz, 2 H), 4,25 - 4,46 (m, 2 H), 5,09 (s, 2 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,81 - 7,02 (m, 2 H), 7,15 - 7,25 (m, 3 H), 7,30 - 7,59 (m, 5 H).

(2) ácido 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico

El 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de

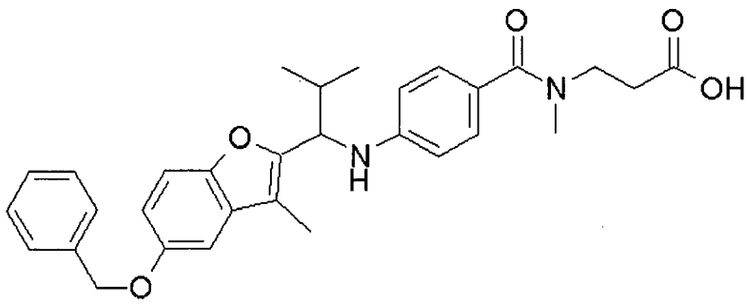
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etilo (1,23 g)ópticamente resuelto en el punto (1) antes mencionado se disolvió en etanol (15 mL), solución acuosa 1 N de hidróxido de sodio (4 mL) se añadió a temperatura ambiente y la mezcla se agitó a 50 °C durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (4 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (1,22 g, 95%, 99,9% ee) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,8 Hz, 3 H), 1,12 (d, J = 6,8 Hz, 3 H), 2,18 - 2,30 (m, 4 H), 2,66 (t, J = 6,2 Hz, 2 H), 3,03 (s, 3 H), 3,69 (t, J = 6,2 Hz, 2 H), 4,32 (d, J = 7,5 Hz, 1 H), 5,08 (s, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,83 - 7,02 (m, 2 H), 7,17 - 7,26 (m, 3 H), 7,30 - 7,53 (m, 5 H).

Ejemplo A87

Ácido 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico



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(1) 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

El 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (3,0 g) sintetizado en el Ejemplo A85(3) se fraccionó por cromatografía líquida de alto rendimiento (columna: CHIRALPAK AD (50mm i.d.×500 mmL, fabricada por Daicel Chemical Industries, Ltd., fase móvil: hexano/etanol (200/800), velocidad de flujo: 60 mL/min, temperatura de la columna: 30 °C). La fracción que contenía una forma ópticamente activa con un tiempo de retención más corto en las condiciones antes mencionadas de la cromatografía líquida de alto rendimiento se concentró para dar el compuesto objeto del título (1,25 g, 99,9% ee).

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,8 Hz, 3 H), 1,12 (d, J = 6,8 Hz, 3 H), 1,23 (t, J = 7,2 Hz, 3 H), 2,13 - 2,33 (m, 4 H), 2,61 (t, J = 7,2 Hz, 2 H), 3,01 (s, 3 H), 3,71 (t, J = 7,2 Hz, 2 H), 4,12 (q, J = 7,2 Hz, 2 H), 4,25 - 4,46 (m, 2 H), 5,09 (s, 2 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,81 - 7,02 (m, 2 H), 7,15 - 7,25 (m, 3 H), 7,30 - 7,59 (m, 5 H).

(2) ácido 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico

El 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (1,25 g) ópticamente resuelto en el punto (1) antes

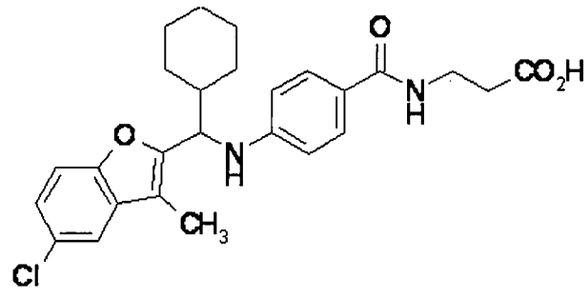
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mencionado se disolvió en etanol (15 mL), una solución acuosa 1 N de hidróxido de sodio (4 mL) se añadió a temperatura ambiente y la mezcla se agitó a 50 °C durante 0,5 h. El etanol se evaporó a presión reducida, el ácido clorhídrico 1 N (4 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (1,08 g, 93%, 99,9% ee) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,8 Hz, 3 H), 1,12 (d, J = 6,8 Hz, 3 H), 2,18 - 2,30 (m, 4 H), 2,66 (t, J = 6,2 Hz, 2 H), 3,03 (s, 3 H), 3,69 (t, J = 6,2 Hz, 2 H), 4,32 (d, J = 7,5 Hz, 1 H), 5,08 (s, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,83 - 7,02 (m, 2 H), 7,17 - 7,26 (m, 3 H), 7,30 - 7,53 (m, 5 H).

Ejemplo A88

Ácido 3-{[(4-{[(5-cloro-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico




(1)5-cloro-N-metoxi-N,3-dimetil-1-benzofuran-2-carboxamida

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A una solución (50 mL) de 1-(5-cloro-2-hidroxifenil)etanona (5,00 g) en tetrahidrofurano se añadieron carbonato de potasio (8,10 g), yoduro de sodio (8,78 g) y 2-cloro-N-metoxi-N-metilacetamida (4,43 g) y la mezcla se agitó durante la noche con calentamiento a reflujo. Insoluble material se filtró y el filtrado se concentró a presión reducida para dar un sólido blanco. A una solución (50 mL) del sólido obtenido en N,N-dimetilformamida se añadió 1,8-diazabiciclo[5,4,0]undec-7-eno (4,38 mL) y la mezcla se agitó a 120 °C durante 2 h. La mezcla de reacción se enfrió hasta temperatura ambiente, el ácido clorhídrico 1 N se añadió y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30% de acetato de etilo/hexano) para dar el compuesto objeto del título (2,15 g, 29%) en forma de un sólido marrón.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,47 (s, 3 H), 3,38 (s, 3 H), 3,86 (s, 3 H), 7,35 (dd, J = 8,9, 1,8 Hz, 1 H), 7,40 (dd, J = 8,9, 0,6 Hz, 1 H), 7,57 (dd, J = 1,8, 0,6 Hz, 1 H).

(2)5-cloro-3-metil-1-benzofuran-2-carbaldehído

A una solución (40 mL) de 5-cloro-N-metoxi-N,3-dimetil-1-benzofuran-2-carboxamida (2,15 g) sintetizado con anterioridad en tetrahidrofurano se añadió hidruro de litio y aluminio (322 mg) a 0 °C y la mezcla se agitó durante 1 h. Se añadió agua (320 µL) para neutralizar la reacción, una solución acuosa 1 N de hidróxido de sodio (320 µL) se añadió y la mezcla se agitó a temperatura ambiente durante 1 h. El

material insoluble resultante se filtró y el filtrado se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (tetrahidrofurano) para dar un sólido de color amarillo pálido. El sólido obtenido se lavó con éter diisopropílico para dar el compuesto objeto del título (1,21 g, 73%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,60 (s, 3 H), 7,43 - 7,51 (m, 2 H), 7,65 - 7,67 (m, 1 H), 10,02 (s, 1 H).

(3)(5-cloro-3-metil-1-benzofuran-2-il)(ciclohexil)metanol

A una solución (10 mL) de 5-cloro-3-metil-1-benzofuran-2-carbaldehído (600 mg) sintetizado con anterioridad en tetrahidrofurano se añadió una solución 1,0 M (4,62 mL) de bromuro de ciclohexilmagnesio en tetrahidrofurano a 0 °C y la mezcla se agitó durante 1 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (15% de acetato de etilo/hexano) para dar el compuesto objeto del título (518 mg, 60%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 - 1,41 (m, 6 H), 1,61 - 1,71 (m, 2 H), 1,75 - 1,98 (m, 3 H), 2,09 - 2,18 (m, 1 H), 2,19 (s, 3 H), 4,52 (dd, J = 8,4, 6,0 Hz, 1 H), 7,20 (dd, J = 8,4, 2,1 Hz, 1 H), 7,33 (dd, J = 8,4, 0,6 Hz, 1 H), 7,42 (dd, J = 2,1, 0,6 Hz, 1 H).

(4)5-cloro-2-[cloro(ciclohexil)metil]-3-metil-1-benzofurano

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A una solución (10 mL) de (5-cloro-3-metil-1-benzofuran-2-il)(ciclohexil)metanol (518 mg) sintetizada con anterioridad en tolueno se añadió cloruro de tionilo (163 µL) y la mezcla se agitó a 100 °C durante 1 h. La mezcla de reacción se vertió en solución saturada acuosa de carbonato ácido de sodio helada y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (553 mg, cuantitativo) en forma de un aceite amarillo pálido.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,83 - 1,48 (m, 6 H), 1,60 - 1,71 (m, 2 H), 1,77 - 1,87 (m, 1 H), 2,10 - 2,24 (m, 4 H), 2,27 - 2,37 (m, 1 H), 4,78 (d, J = 9,6 Hz, 1 H), 7,20 - 7,26 (m, 1 H), 7,34 - 7,38 (m, 1 H), 7,42 - 7,44 (m, 1 H).
(5) ácido 3-{[(4-{[(5-cloro-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico

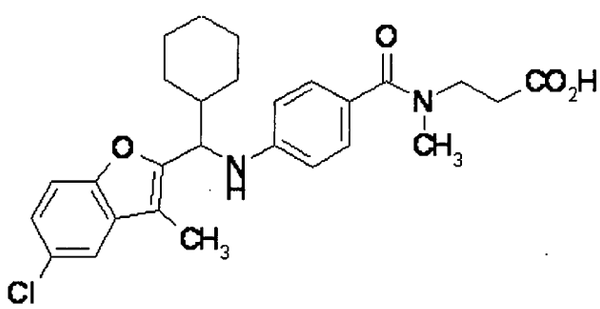
Una mezcla de 5-cloro-2-[cloro(ciclohexil)metil]-3-metil-1-benzofurano (270 mg) sintetizado con anterioridad, 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (215 mg) sintetizado en el Ejemplo 1(2), se añadieron yoduro de sodio (204 mg), carbonato de sodio (144 mg) y N,N-dimetilformamida (10 mL) se agitó durante la noche a 80 °C. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de hidrógeno-carbonato de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (50% de acetato de

etilo/hexano) para dar un aceite de color amarillo pálido. A una mezcla del aceite obtenido, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y la mezcla de reacción se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (132 mg, 31%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,35 (m, 5 H), 1,44 - 1,55 (m, 1 H), 1,60 - 1,96 (m, 4 H), 2,01 - 2,12 (m, 1 H), 2,20 (s, 3 H), 2,54 - 2,67 (m, 2 H), 3,56 - 3,68 (m, 2 H), 4,37 (d, J = 7,9 Hz, 1 H), 6,50 - 6,66 (m, 3 H), 7,12 - 7,18 (m, 1 H), 7,23 - 7,30 (m, 1 H), 7,37 (d, J = 1,9 Hz, 1 H), 7,52 (d, J = 8,7 Hz, 2 H).

Ejemplo A89

Ácido 3-{[(4-{[(5-cloro-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico



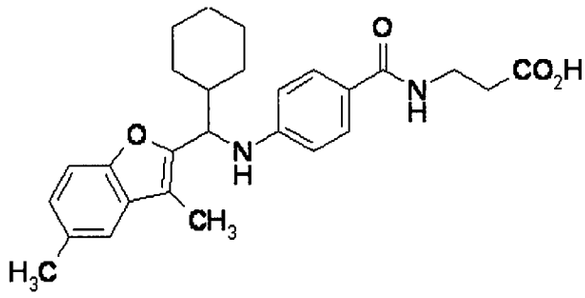
Una mezcla de 5-cloro-2-[cloro(ciclohexil)metil]-3-metil-1-benzofurano (283 mg) sintetizado en el Ejemplo A88(4), 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (238 mg) sintetizado en el Ejemplo 2(2), yoduro de sodio (214 mg), carbonato de sodio (152 mg) y N,N-dimetilformamida (10 mL) se agitó durante la noche a 80 °C. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de hidrógeno-carbonato de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (40% de acetato de etilo/hexano) para dar un aceite de color amarillo pálido. A una mezcla del aceite obtenido, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 1,5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (113 mg, 25%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,38 (m, 5 H), 1,45 - 1,56 (m, 1 H), 1,61 - 1,97 (m, 4 H), 2,02 - 2,13 (m, 1 H), 2,21 (s, 3 H), 2,60 - 2,69 (m, 2 H), 3,01 (s, 3 H), 3,68 (t, J = 6,2 Hz, 2 H), 4,36 (d, J = 7,9 Hz, 1 H), 6,54 (d, J = 8,7 Hz, 2 H), 7,13 - 7,19 (m, 1 H), 7,20 - 7,31 (m, 3 H), 7,38 (d, J = 1,9 Hz, 1 H).

Ejemplo A90

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Ácido 3-{[(4-{[ciclohexil(3,5-dimetil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico




(1)N-metoxi-N,3,5-trimetil-1-benzofuran-2-carboxamida

A una solución (50 mL) de 1-(2-hidroxi-5-metilfenil)etanona (5,00 g) en N,N-dimetilformamida se añadieron carbonato de potasio (9,20 g), yoduro de sodio (9,98 g) y 2-cloro-N-metoxi-N-metilacetamida (5,04 g) y la mezcla se agitó a 50 °C durante 5 h, luego a 80 °C durante la noche. El material insoluble se filtró, se añadió 1,8-diazabiciclo[5,4,0]undec-7-eno (5,00 mL) al filtrado y la mezcla se agitó a 120 °C durante 2 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (20% de acetato de etilo/hexano) para dar el compuesto objeto del título (3,78 g, 49%) en forma de un aceite marrón.

1353

$^1$H RMN (300 MHz, $CDCl_3$) δ 2,47 (s, 3 H), 2,49 (s, 3 H), 3,38 (s, 3 H), 3,86 (s, 3 H), 7,19 - 7,24 (m, 1 H), 7,32 - 7,34 (m, 1 H), 7,35 - 7,39 (m, 1 H).

(2)3,5-dimetil-1-benzofuran-2-carbaldehído

A una solución (50 mL) de N-metoxi-N,3,5-trimetil-1-benzofuran-2-carboxamida (3,78 g) sintetizado con anterioridad en tetrahidrofurano se añadió hidruro de litio y aluminio (307 mg) a -78 °C y la mezcla se agitó durante 2 h. Se añadió agua (350 µL) para neutralizar la reacción, una solución acuosa 1 N de hidróxido de sodio (700 µL) se añadió y la mezcla se agitó a temperatura ambiente durante 1 h. El material insoluble resultante se filtró y el filtrado se concentró a presión reducida. El residuo se lavó con hexano para dar el compuesto objeto del título (2,08 g, 74%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,48 (s, 3 H), 2,60 (s, 3 H), 7,30 - 7,35 (m, 1 H), 7,40 - 7,47 (m, 2 H), 10,01 (s, 1 H).

(3)ciclohexil(3,5-dimetil-1-benzofuran-2-il)metanol

A una solución (20 mL) de 3,5-dimetil-1-benzofuran-2-carbaldehído (1,00 g) sintetizada con anterioridad en tetrahidrofurano se añadió una solución 1,0 M (8,61 mL) de bromuro de ciclohexilmagnesio en tetrahidrofurano a 0 °C y la mezcla se agitó durante 1 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción, el tetrahidrofurano se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se

concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (25% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,13 g, 76%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,83 - 0,99 (m, 1 H), 1,00 - 1,44 (m, 5 H), 1,58 - 1,70 (m, 2 H), 1,74 - 1,98 (m, 3 H), 2,09 - 2,22 (m, 4 H), 2,45 (s, 3 H), 4,51 (dd, J = 8,5, 5,9 Hz, 1 H), 7,03 - 7,11 (m, 1 H), 7,23 - 7,33 (m, 2 H).

(4)2-[cloro(ciclohexil)metil]-3,5-dimetil-1-benzofurano

A una solución (20 mL) de ciclohexil(3,5-dimetil-1-benzofuran-2-il)metanol (1,13 g) sintetizado con anterioridad en tolueno se añadieron piridina (424 µL) y cloruro de tionilo (382 µL) y la mezcla se agitó a temperatura ambiente durante 5 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (1,12 g, 93%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,82 - 0,97 (m, 1 H), 1,00 - 1,40 (m, 4 H), 1,41 - 1,51 (m, 1 H), 1,59 - 1,70 (m, 2 H), 1,76 - 1,87 (m, 1 H), 2,11 - 2,25 (m, 4 H), 2,28 - 2,38 (m, 1 H), 2,44 (s, 3 H), 4,80 (d, J = 9,3 Hz, 1 H), 7,07 - 7,12 (m, 1 H), 7,23 - 7,26 (m, 1 H), 7,32 (d, J = 8,4 Hz, 1 H).

(5) ácido 3-{[(4-{[ciclohexil(3,5-dimetil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico

Una mezcla de 2-[cloro(ciclohexil)metil]-3,5-dimetil-1-benzofurano (400 mg) sintetizado con anterioridad, 3-{[(4-

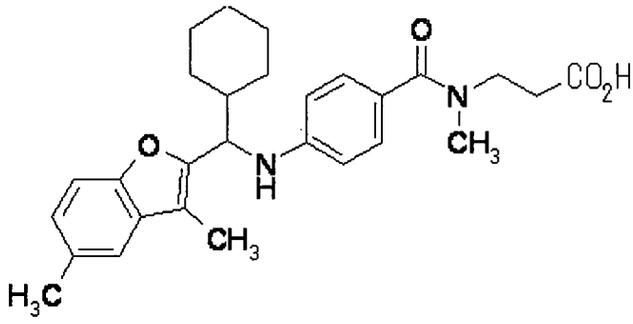
aminofenil)carbonil]amino}propanoato de etilo (343 mg) sintetizado en el Ejemplo 1(2), yoduro de sodio (327 mg), carbonato de sodio (231 mg) y N,N-dimetilformamida (10 mL) se agitó a 80 °C durante 5 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (45% de acetato de etilo/hexano) para dar un aceite amarillo. A una mezcla del aceite obtenido, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (436 mg, 67%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,36 (m, 5 H), 1,47 - 1,58 (m, 1 H), 1,59 - 1,97 (m, 4 H), 2,02 - 2,12 (m, 1 H), 2,22 (s, 3 H), 2,42 (s, 3 H), 2,61 - 2,69 (m, 2 H), 3,60 - 3,70 (m, 2 H), 4,38 (d, J = 8,0 Hz, 1 H), 6,49 - 6,60 (m, 3 H), 7,00 - 7,06 (m, 1 H), 7,19 - 7,24 (m, 2 H), 7,52 (d, J = 7,6 Hz, 2 H).

Ejemplo A91

Ácido 3-{[(4-{[ciclohexil(3,5-dimetil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

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(1) 3-{[(4-{[ciclohexil(3,5-dimetil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

Una mezcla de 2-[cloro(ciclohexil)metil]-3,5-dimetil-1-benzofurano (400 mg) sintetizado en el Ejemplo A90(4), 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (363 mg) sintetizado en el Ejemplo 2(2), yoduro de sodio (327 mg), carbonato de sodio (231 mg) y N,N-dimetilformamida (10 mL) se agitó a 80 °C durante 5 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (45% de acetato de etilo/hexano) para dar el compuesto objeto del título (471 mg, 66%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,36 (m, 8 H), 1,48 - 1,59 (m, 1 H), 1,60 - 1,96 (m, 4 H), 2,03 - 2,13 (m, 1 H), 2,22 (s, 3 H), 2,42 (s, 3 H), 2,57 - 2,65 (m, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,1 Hz, 2 H), 4,07 - 4,17 (m, 2 H), 4,32 -

4,40 (m, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 7,03 (dd, J = 8,3, 1,3 Hz, 1 H), 7,17 - 7,24 (m, 4 H).

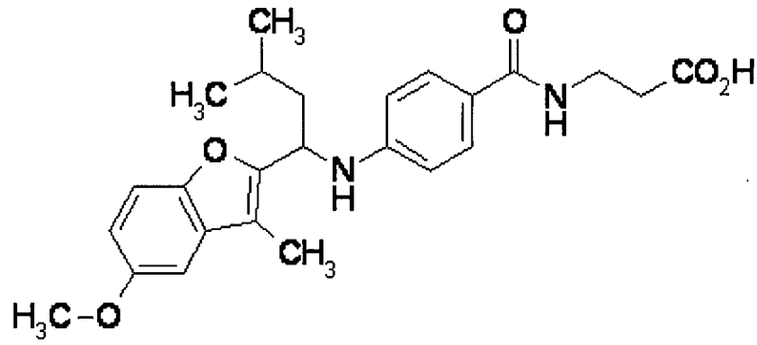
(2) ácido 3-{[(4-{[ciclohexil(3,5-dimetil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

A una mezcla de 3-{[(4-{[ciclohexil(3,5-dimetil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (471 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 3 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (407 mg, 92%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,37 (m, 5 H), 1,47 - 1,58 (m, 1 H), 1,60 - 1,97 (m, 4 H), 2,02 - 2,14 (m, 1 H), 2,23 (s, 3 H), 2,42 (s, 3 H), 2,62 - 2,73 (m, 2 H), 3,04 (s, 3 H), 3,70 (t, J = 6,4 Hz, 2 H), 4,37 (d, J = 8,0 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 7,00 - 7,06 (m, 1 H), 7,19 - 7,28 (m, 4 H).

Ejemplo A92

Ácido 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil]amino}propanoico

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(1)1-(5-metoxi-3-metil-1-benzofuran-2-il)-3-metilbutan-1-ol

A una solución (40 mL) de 5-metoxi-3-metil-1-benzofuran-2-carbaldehído (1,91 g) sintetizado en el Ejemplo A27(2) en tetrahidrofurano se añadió una solución (15,0 mL) de 1,0M bromuro de isobutilmagnesio en tetrahidrofurano a 0 °C y la mezcla se agitó durante 1 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción, el tetrahidrofurano se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (20% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,53 g, 62%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 (d, J = 6,6 Hz, 3 H), 0,95 (d, J = 6,6 Hz, 3 H), 1,54 - 1,69 (m, 1 H), 1,74 - 1,96 (m, 3 H), 2,23 (s, 3 H), 3,85 (s, 3 H), 4,88 - 4,97 (m, 1 H), 6,86 (dd, J = 8,6, 2,7 Hz, 1 H), 6,91 (d, J = 2,7 Hz, 1 H), 7,30 (d, J = 8,6 Hz, 1 H).

(2)2-(1-cloro-3-metilbutil)-5-metoxi-3-metil-1-benzofurano

A una solución (10 mL) de 1-(5-metoxi-3-metil-1-benzofuran-2-il)-3-metilbutan-1-ol (761 mg) sintetizado con anterioridad en tolueno se añadieron piridina (297 µL) y cloruro de tionilo (268 µL) y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (769 mg, 94%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 - 0,96 (m, 3 H), 1,12 (d, J = 6,8 Hz, 3 H), 1,58 - 1,75 (m, 1 H), 2,15 (d, J = 7,9 Hz, 2 H), 2,24 (s, 3 H), 3,86 (s, 3 H), 5,20 (t, J = 7,8 Hz, 1 H), 6,86 - 6,93 (m, 2 H), 7,34 (d, J = 9,4 Hz, 1 H).

(3) 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil]amino}propanoato de etilo

Una mezcla de 2-(1-cloro-3-metilbutil)-5-metoxi-3-metil-1-benzofurano (380 mg) sintetizado con anterioridad, 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (350 mg) sintetizado en el Ejemplo 1(2), yoduro de sodio (443 mg), carbonato de sodio (314 mg) y N,N-dimetilformamida (10 mL) se agitó a 80 °C durante 5 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (50% de acetato de etilo/hexano) para dar el

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compuesto objeto del título (266 mg, 40%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,8 Hz, 3 H), 1,00 (d, J = 6,8 Hz, 3 H), 1,20 - 1,30 (m, 3 H), 1,49 - 1,64 (m, 1 H), 1,79 - 1,91 (m, 2 H), 2,26 (s, 3 H), 2,59 (t, J = 5,9 Hz, 2 H), 3,62 - 3,71 (m, 2 H), 3,83 (s, 3 H), 4,07 - 4,21 (m, 2 H), 4,30 - 4,44 (m, 1 H), 4,70 (t, J = 7,4 Hz, 1 H), 6,56 - 6,63 (m, 3 H), 6,80 - 6,85 (m, 1 H), 6,88 (d, J = 2,3 Hz, 1 H), 7,25 (d, J = 8,7 Hz, 1 H), 7,56 (d, J = 8,7 Hz, 2 H).

(4) ácido 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil]amino}propanoico

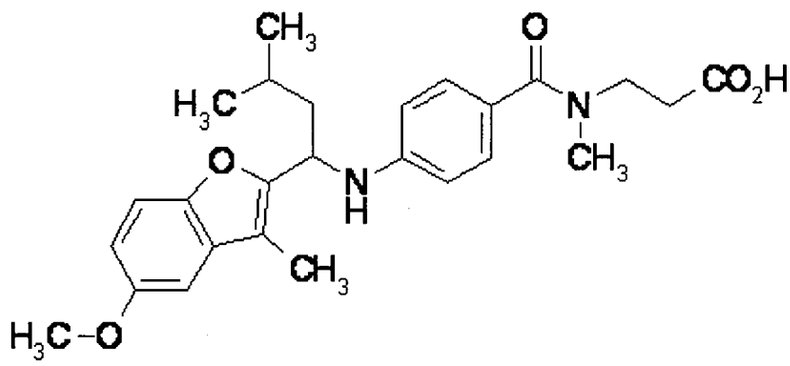
A una mezcla de 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil]amino}propanoato de etilo (266 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (216 mg, 86%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 (d, J = 6,4 Hz, 3 H), 0,99 (d, J = 6,4 Hz, 3 H), 1,48 - 1,64 (m, 1 H), 1,76 - 1,93 (m, 2 H), 2,25 (s, 3 H), 2,63 (t, J = 5,7 Hz, 2 H), 3,59 - 3,69 (m, 2 H), 3,83 (s, 3 H), 4,70 (t, J = 7,4 Hz, 1 H), 6,54 - 6,65 (m, 3 H), 6,78 - 6,85 (m, 1 H), 6,87 (d, J = 2,7 Hz, 1 H), 7,20 - 7,30 (m, 1 H), 7,53 (d, J = 8,7 Hz, 2 H).

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Ejemplo A93

Ácido 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil](metil)amino}propanoico



(1) 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil](metil)amino}propanoato de etilo

Una mezcla de 2-(1-cloro-3-metilbutil)-5-metoxi-3-metil-1-benzofurano (380 mg) sintetizado en el Ejemplo A92(2), 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (370 mg) sintetizado en el Ejemplo 2(2), yoduro de sodio (443 mg), carbonato de sodio (314 mg) y N,N-dimetilformamida (10 mL) se agitó a 80 °C durante 5 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (60% de acetato de etilo/hexano) para dar el compuesto objeto del título (350 mg, 51%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,4 Hz, 3 H), 1,00 (d, J = 6,8 Hz, 3 H), 1,19 - 1,30 (m, 3 H), 1,49 - 1,64 (m, 1

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H), 1,80 - 1,89 (m, 2 H), 2,26 (s, 3 H), 2,61 (t, J = 7,0 Hz, 2 H), 3,01 (s, 3 H), 3,71 (t, J = 7,0 Hz, 2 H), 3,84 (s, 3 H), 4,07 - 4,17 (m, 2 H), 4,68 (t, J = 7,4 Hz, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 6,80 - 6,86 (m, 1 H), 6,88 (d, J = 2,3 Hz, 1 H), 7,23 (d, J = 8,7 Hz, 2 H), 7,26 (d, J = 8,7 Hz, 1 H).

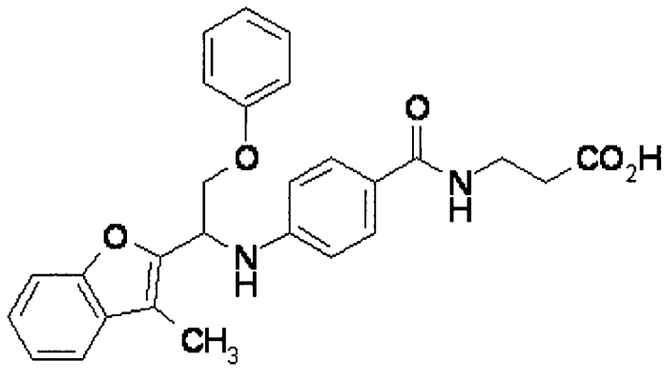
(2) ácido 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil](metil)amino}propanoico

A una mezcla de 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil](metil)amino}propanoato de etilo (350 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (308 mg, 94%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,4 Hz, 3 H), 1,00 (d, J = 6,4 Hz, 3 H), 1,48 - 1,65 (m, 1 H), 1,81 - 1,89 (m, 2 H), 2,26 (s, 3 H), 2,65 - 2,75 (m, 2 H), 3,05 (s, 3 H), 3,71 (t, J = 6,4 Hz, 2 H), 3,84 (s, 3 H), 4,69 (t, J = 7,4 Hz, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 6,80 - 6,86 (m, 1 H), 6,88 (d, J = 2,3 Hz, 1 H), 7,23 - 7,30 (m, 3 H).

Ejemplo A94

Ácido 3-{[(4-{[1-(3-metil-1-benzofuran-2-il)-2-fenoxietil]amino}fenil)carbonil]amino}propanoico

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(1) 1-(3-metil-1-benzofuran-2-il)-2-fenoxietanona

A una mezcla de 2-bromo-1-(3-metil-1-benzofuran-2-il)etanona (1,00 g), fenol (446 mg) y N,N-dimetilformamida (20 mL) se añadió carbonato de potasio (655 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (10% de acetato de etilo/hexano) para dar el compuesto objeto del título (697 mg, 66%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,65 (s, 3 H), 5,36 (s, 2 H), 6,81 - 6,86 (m, 1 H), 6,98 - 7,06 (m, 2 H), 7,20 - 7,39 (m, 3 H), 7,51 - 7,57 (m, 2 H), 7,67 - 7,73 (m, 1 H).

(2) 4-{[1-(3-metil-1-benzofuran-2-il)-2-fenoxietil]amino}benzoato de metilo

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A una mezcla de 1-(3-metil-1-benzofuran-2-il)-2-fenoxietanona (697 mg) sintetizada con anterioridad, 4-aminobenzoato de metilo (399 mg), trietilamina (2,93 mL) y cloruro de metileno (10 mL) se añadió cloruro de titanio (IV) (344 µL) a 0 °C bajo una atmósfera de argón y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción, el cloruro de metileno se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (20 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (2 mL) y cianoborohidruro de sodio (329 mg) y la mezcla se agitó a temperatura ambiente durante 15 min. Ácido trifluoroacético (2 mL) se añadió a la mezcla de reacción y la mezcla luego se agitó a temperatura ambiente durante 3 h. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (25% de acetato de etilo/hexano) para dar el compuesto objeto del título (279 mg, 27%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,29 (s, 3 H), 3,83 (s, 3 H), 4,32 - 4,44 (m, 2 H), 4,91 (d, J = 6,6 Hz, 1 H), 5,08 - 5,16 (m, 1 H), 6,66 (d, J = 8,9 Hz, 1 H), 6,81 - 6,99 (m, 3 H),

7,18 - 7,31 (m, 4 H), 7,38 - 7,48 (m, 2 H), 7,84 (d, J = 8,9 Hz, 2 H).

(3) ácido 4-{[1-(3-metil-1-benzofuran-2-il)-2-fenoxietil]amino}benzoico

A una mezcla de 4-{[1-(3-metil-1-benzofuran-2-il)-2-fenoxietil]amino}benzoato de metilo (279 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (5,00 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (5,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (220 mg, 82%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,30 (s, 3 H), 4,32 - 4,46 (m, 2 H), 4,92 - 5,03 (m, 1 H), 5,09 - 5,20 (m, 1 H), 6,69 (d, J = 9,1 Hz, 2 H), 6,90 (d, J = 7,6 Hz, 2 H), 6,93 - 7,01 (m, 1 H), 7,19 - 7,34 (m, 4 H), 7,38 - 7,51 (m, 2 H), 7,90 (d, J = 8,7 Hz, 2 H).

(4) 3-{[(4-{[1-(3-metil-1-benzofuran-2-il)-2-fenoxietil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[1-(3-metil-1-benzofuran-2-il)-2-fenoxietil]amino}benzoico (100 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (59,4 mg), monohidrato de 1-hidroxibenzotriazol (59,3 mg), trietilamina (72 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (74,2 mg) y la mezcla se agitó durante la noche a temperatura

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ambiente. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (45% de acetato de etilo/hexano) para dar el compuesto objeto del título (63,0 mg, 50%) en forma de un aceite amarillo pálido. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,25 (t, J = 7,2 Hz, 3 H), 2,29 (s, 3 H), 2,59 (t, J = 5,8 Hz, 2 H), 3,62 - 3,72 (m, 2 H), 4,14 (q, J = 7,2 Hz, 2 H), 4,31 - 4,44 (m, 2 H), 4,78 - 4,88 (m, 1 H), 5,06 - 5,15 (m, 1 H), 6,60 - 6,71 (m, 3 H), 6,89 (dd, J = 8,8, 1,0 Hz, 2 H), 6,93 - 7,00 (m, 1 H), 7,18 - 7,31 (m, 4 H), 7,38 - 7,49 (m, 2 H), 7,59 (d, J = 8,9 Hz, 2 H).

(5) ácido 3-{[(4-{[1-(3-metil-1-benzofuran-2-il)-2-fenoxietil]amino}fenil)carbonil]amino}propanoico

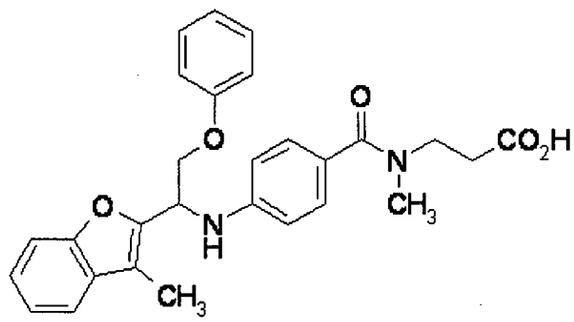
A una mezcla de 3-{[(4-{[1-(3-metil-1-benzofuran-2-il)-2-fenoxietil]amino}fenil)carbonil]amino}propanoato de etilo (63,0 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y el ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (57,5 mg, 97%) en forma de un sólido de color marrón pálido.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,29 (s, 3 H), 2,68 (t, J = 5,9 Hz, 2 H), 3,63 - 3,72 (m, 2 H), 4,32 - 4,44 (m, 2 H), 5,10 (t, J = 6,1 Hz, 1 H), 6,58 (t, J = 5,7 Hz, 1 H), 6,67 (d, J = 8,7 Hz, 2 H), 6,87 - 6,92 (m, 2 H), 6,93 - 7,00 (m, 1 H), 7,18 - 7,31 (m, 4 H), 7,38 - 7,43 (m, 1 H), 7,44 - 7,49 (m, 1 H), 7,58 (d, J = 8,7 Hz, 2 H).

Ejemplo A95

Ácido 3-{metil[(4-{[1-(3-metil-1-benzofuran-2-il)-2-fenoxietil]amino}fenil)carbonil]amino}propanoico




(1) 3-{metil[(4-{[1-(3-metil-1-benzofuran-2-il)-2-fenoxietil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[1-(3-metil-1-benzofuran-2-il)-2-fenoxietil]amino}benzoico (100 mg) sintetizado en el Ejemplo A94(3), 3-(metilamino)propanoato de etilo (50,8 mg), monohidrato de 1-hidroxibenzotriazol (59,3 mg), trietilamina (54 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (74,2 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y

la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (50% de acetato de etilo/hexano) para dar el compuesto objeto del título (82,5 mg, 64%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,23 (t, J = 7,2 Hz, 3 H), 2,29 (s, 3 H), 2,57 - 2,67 (m, 2 H), 3,02 (s, 3 H), 3,72 (t, J = 7,1 Hz, 2 H), 4,12 (q, J = 7,2 Hz, 2 H), 4,30 - 4,44 (m, 2 H), 5,08 (t, J = 6,0 Hz, 1 H), 6,66 (d, J = 8,7 Hz, 2 H), 6,90 (dd, J = 8,7, 0,9 Hz, 2 H), 6,93 - 7,01 (m, 1 H), 7,19 - 7,32 (m, 6 H), 7,38 - 7,50 (m, 2 H).

(2) ácido 3-{metil[(4-{[1-(3-metil-1-benzofuran-2-il)-2-fenoxietil]amino}fenil)carbonil]amino}propanoico

A una mezcla de 3-{metil[(4-{[1-(3-metil-1-benzofuran-2-il)-2-fenoxietil]amino}fenil)carbonil]amino}propanoato de etilo (82,5 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (54,8 mg, 70%) en forma de un sólido blanco.

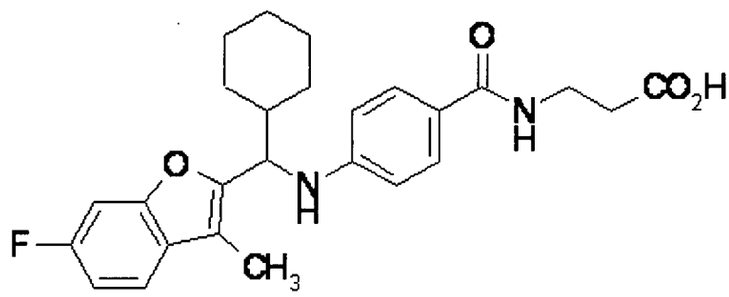
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,29 (s, 3 H), 2,61 - 2,72 (m, 2 H), 3,04 (s, 3 H), 3,71 (t, J = 6,6 Hz, 2 H), 4,30 - 4,42 (m,

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2 H), 5,08 (t, J = 6,1 Hz, 1 H), 6,66 (d, J = 8,7 Hz, 2 H), 6,86 - 6,92 (m, 2 H), 6,92 - 7,00 (m, 1 H), 7,18 - 7,31 (m, 6 H), 7,38 - 7,43 (m, 1 H), 7,44 - 7,49 (m, 1 H).

Ejemplo A96

Ácido 3-{[(4-{[ciclohexil(6-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico



(1)6-fluoro-N-metoxi-N,3-dimetil-1-benzofuran-2-carboxamida

A una solución (50 mL) de 1-(4-fluoro-2-hidroxifenil)etanona (5,00 g) en N,N-dimetilformamida se añadieron 2-cloro-N-metoxi-N-metilacetamida (4,90 g), yoduro de sodio (9,71 g) y carbonato de potasio (8,96 g) y la mezcla se agitó durante la noche a 80 °C. La mezcla de reacción se enfrió hasta temperatura ambiente, el material insoluble se filtró. 1,8-diazabiciclo[5,4,0]undec-7-eno (4,85 mL) se añadió al filtrado y la mezcla se agitó a 120 °C durante 2 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (25% de acetato de

etilo/hexano) para dar el compuesto objeto del título (3,65 g, 47%) en forma de un aceite de color marrón pálido

$^1$H RMN (300 MHz, $CDCl_3$) δ 2,50 (s, 3 H), 3,38 (s, 3 H), 3,87 (s, 3 H), 7,01 - 7,11 (m, 1 H), 7,18 (dd, J = 8,8, 1,9 Hz, 1 H), 7,54 (dd, J = 8,8, 5,5 Hz, 1 H).

(2)6-fluoro-3-metil-1-benzofuran-2-carbaldehído

A una solución (50 mL) de 6-fluoro-N-metoxi-N,3-dimetil-1-benzofuran-2-carboxamida (3,65 g) sintetizada con anterioridad en tetrahidrofurano se añadió hidruro de litio y aluminio (292 mg) a 0 °C y la mezcla se agitó durante 1 h. Se añadió agua (300 µL) para neutralizar la reacción, una solución acuosa 1 N de hidróxido de sodio (600 µL) se añadió y la mezcla se agitó a temperatura ambiente durante 1 h. El material insoluble resultante se filtró y el filtrado se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (20% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,88 g, 69%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,62 (s, 3 H), 7,07 - 7,15 (m, 1 H), 7,22 - 7,28 (m, 1 H), 7,65 (dd, J = 8,8, 5,4 Hz, 1 H), 9,99 (s, 1 H).

(3)ciclohexil(6-fluoro-3-metil-1-benzofuran-2-il)metanol

A una solución (20 mL) de 6-fluoro-3-metil-1-benzofuran-2-carbaldehído (940 mg) sintetizado con anterioridad en tetrahidrofurano se añadió una solución 1,0 M (7,92 mL) de bromuro de ciclohexilmagnesio en tetrahidrofurano a 0 °C y la mezcla se agitó durante 1 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción,

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el tetrahidrofurano se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (15% de acetato de etilo/hexano) para dar el compuesto objeto del título (931 mg, 67%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 - 1,00 (m, 1 H), 1,00 - 1,44 (m, 5 H), 1,60 - 1,71 (m, 2 H), 1,76 - 1,99 (m, 3 H), 2,10 - 2,23 (m, 4 H), 4,50 (dd, J = 8,3, 6,1 Hz, 1 H), 6,94 - 7,02 (m, 1 H), 7,10 - 7,17 (m, 1 H), 7,34 - 7,40 (m, 1 H).

(4)2-[cloro(ciclohexil)metil]-6-fluoro-3-metil-1-benzofurano

A una solución (20 mL) de ciclohexil(6-fluoro-3-metil-1-benzofuran-2-il)metanol (931 mg) sintetizado con anterioridad en tolueno se añadió cloruro de tionilo (311 µL) y la mezcla se agitó a 100 °C durante 1 h. La mezcla de reacción se vertió en solución saturada acuosa de carbonato ácido de sodio helada y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (945 mg, 95%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,82 - 0,98 (m, 1 H), 0,99 - 1,52 (m, 5 H), 1,60 - 1,72 (m, 2 H), 1,76 - 1,89 (m, 1 H), 2,11 - 2,25 (m, 4 H), 2,26 - 2,39 (m, 1 H), 4,79 (d, J = 9,6 Hz, 1 H), 6,96 - 7,04 (m, 1 H), 7,15 - 7,20 (m, 1 H), 7,35 - 7,41 (m, 1 H).

(5) ácido 4-{[ciclohexil(6-fluoro-3-metil-1-benzofuran-2-il)metil]amino}benzoico

A una mezcla de 2-[cloro(ciclohexil)metil]-6-fluoro-3-metil-1-benzofurano (945 mg) sintetizado con anterioridad, 4-aminobenzoato de metilo (508 mg), yoduro de sodio (1,01 g) y N,N-dimetilformamida (10 mL) se añadió carbonato de sodio (712 mg) y la mezcla se agitó a 80 °C durante la noche. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (20% de acetato de etilo/hexano) para dar un sólido amarillo. A una mezcla del sólido obtenido, tetrahidrofurano (20 mL) y etanol (20 mL) se añadió solución acuosa 1 N de hidróxido de sodio (10,0 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (40 mL) y ácido clorhídrico 1 N (10,0 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (722 mg, 56%) en forma de un sólido marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,38 (m, 5 H), 1,46 - 1,57 (m, 1 H), 1,61 - 1,98 (m, 4 H), 2,02 - 2,13 (m, 1 H), 2,25 (s, 3 H), 4,40 (d, J = 7,9 Hz, 1 H), 4,51 - 4,74 (m, 1 H), 6,57 (d, J = 8,8 Hz, 2 H), 6,91 - 7,00 (m, 1 H), 7,06 - 7,12 (m, 1 H), 7,29 - 7,36 (m, 1 H), 7,85 (d, J = 8,8 Hz, 2 H).

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(6) 3-{[(4-{[ciclohexil(6-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclohexil(6-fluoro-3-metil-1-benzofuran-2-il)metil]amino}benzoico (350 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (212 mg), monohidrato de 1-hidroxibenzotriazol (211 mg), trietilamina (383 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (265 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de hidrógeno-carbonato de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (50% de acetato de etilo/hexano) para dar el compuesto objeto del título (403 mg, 91%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,39 (m, 8 H), 1,46 - 1,57 (m, 1 H), 1,62 - 1,97 (m, 4 H), 2,03 - 2,14 (m, 1 H), 2,24 (s, 3 H), 2,58 (t, J = 5,9 Hz, 2 H), 3,61 - 3,70 (m, 2 H), 4,14 (q, J = 7,2 Hz, 2 H), 4,32 - 4,47 (m, 2 H), 6,54 - 6,63 (m, 3 H), 6,90 - 7,00 (m, 1 H), 7,05 - 7,12 (m, 1 H), 7,28 - 7,35 (m, 1 H), 7,55 (d, J = 8,9 Hz, 2 H).

(7) ácido 3-{[(4-{[ciclohexil(6-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico

A una mezcla de 3-{[(4-{[ciclohexil(6-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoato

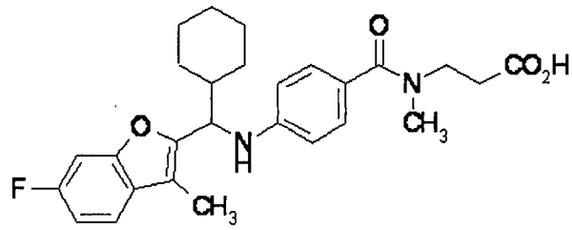
1373

de etilo (403 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 3 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (355 mg, 93%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,37 (m, 5 H), 1,44 - 1,56 (m, 1 H), 1,60 - 1,96 (m, 4 H), 2,00 - 2,12 (m, 1 H), 2,22 (s, 3 H), 2,53 - 2,66 (m, 2 H), 3,54 - 3,67 (m, 2 H), 4,35 (d, J = 8,3 Hz, 1 H), 6,48 - 6,64 (m, 3 H), 6,89 - 6,99 (m, 1 H), 7,03 - 7,11 (m, 1 H), 7,27 - 7,34 (m, 1 H), 7,52 (d, J = 8,7 Hz, 2 H).

Ejemplo A97

Ácido 3-{[(4-{[ciclohexil(6-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico



(1) 3-{[(4-{[ciclohexil(6-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclohexil(6-fluoro-3-metil-1-benzofuran-2-il)metil]amino}benzoico (350 mg) sintetizado en el Ejemplo A96(5), 3-(metilamino)propanoato de etilo (181 mg), monohidrato de 1-hidroxibenzotriazol (211 mg), trietilamina (383 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (265 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (50% de acetato de etilo/hexano) para dar el compuesto objeto del título (432 mg, 95%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,37 (m, 8 H), 1,46 - 1,56 (m, 1 H), 1,60 - 1,96 (m, 4 H), 2,02 - 2,14 (m, 1 H), 2,23 (s, 3 H), 2,61 (t, J = 6,9 Hz, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 6,9 Hz, 2 H), 4,07 - 4,17 (m, 2 H), 4,27 - 4,39 (m, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,91 - 7,00 (m, 1 H), 7,06 - 7,12 (m, 1 H), 7,21 (d, J = 8,7 Hz, 2 H), 7,28 - 7,35 (m, 1 H).

(2) ácido 3-{[(4-{[ciclohexil(6-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

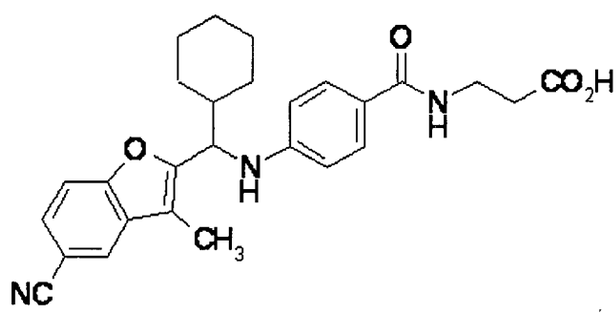
1375

A una mezcla de 3-{[(4-{[ciclohexil(6-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (432 mg) sintetizado con anterioridad, tetrahidrofurano (10 mL) y etanol (10 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 4 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (367 mg, 90%) en forma de un sólido de color rojo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,37 (m, 5 H), 1,46 - 1,57 (m, 1 H), 1,61 - 1,96 (m, 4 H), 2,03 - 2,14 (m, 1 H), 2,23 (s, 3 H), 2,67 (t, J = 6,4 Hz, 2 H), 3,04 (s, 3 H), 3,70 (t, J = 6,4 Hz, 2 H), 4,35 (d, J = 8,0 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,91 - 7,00 (m, 1 H), 7,06 - 7,12 (m, 1 H), 7,21 - 7,28 (m, 2 H), 7,29 - 7,36 (m, 1 H).

Ejemplo A98

Ácido 3-{[(4-{[(5-ciano-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico



1376

(1) 5-bromo-3-metil-1-benzofuran-2-carboxilato de metilo

A una solución (100 mL) de 1-(5-bromo-2-hidroxifenil)etanona (10,0 g) en N,N-dimetilformamida se añadieron bromoacetato de metilo (4,85 mL) y carbonato de potasio (12,9 g) y la mezcla se agitó durante la noche a temperatura ambiente. El material insoluble se filtró, se añadió 1,8-diazabiciclo[5,4,0]undec-7-eno (6,95 mL) al filtrado y la mezcla se agitó a 120 °C durante 2 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (10% de acetato de etilo/hexano) para dar el compuesto objeto del título (6,06 g, 48%) en forma de un sólido de color marrón pálido.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,56 (s, 3 H), 3,99 (s, 3 H), 7,39 - 7,44 (m, 1 H), 7,51 - 7,56 (m, 1 H), 7,76 (d, J = 1,9 Hz, 1 H).

(2) 5-ciano-3-metil-1-benzofuran-2-carboxilato de metilo

A una mezcla de 5-bromo-3-metil-1-benzofuran-2-carboxilato de metilo (6,06 g) sintetizado con anterioridad, cianuro de zinc (2,64 g) y N,N-dimetilformamida (60 mL) se añadió tetrakis(trifenilfosfina)paladio (0) (1,31 g) y la mezcla se desgasificó y se agitó bajo una atmósfera de argón a 80 °C durante la noche. Se añadió agua para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se

lavó con éter diisopropílico para dar el compuesto objeto del título (4,20 g, 87%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,61 (s, 3 H), 4,01 (s, 3 H), 7,61 - 7,66 (m, 1 H), 7,69 - 7,74 (m, 1 H), 8,00 (d, J = 0,9 Hz, 1 H).

(3) ácido 5-ciano-3-metil-1-benzofuran-2-carboxílico

A una mezcla de 5-ciano-3-metil-1-benzofuran-2-carboxilato de metilo (4,20 g) sintetizado con anterioridad, tetrahidrofurano (80 mL), agua (20 mL) y metanol (20 mL) se añadió hidróxido de litio monohidratado (1,64 g) y la mezcla se agitó durante la noche a temperatura ambiente y se concentró a presión reducida. Se añadió ácido clorhídrico 1 N al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con éter diisopropílico para dar el compuesto objeto del título (3,58 g, 91%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, DMSO-d6) δ ppm 2,55 (s, 3 H), 7,85 - 7,89 (m, 1 H), 7,91 - 7,95 (m, 1 H), 8,44 - 8,47 (m, 1 H), 13,76 (br s, 1 H).

(4) 2-formil-3-metil-1-benzofuran-5-carbonitrilo

A ácido 5-ciano-3-metil-1-benzofuran-2-carboxílico (2,58 g) sintetizado con anterioridad en tetrahidrofurano (30 mL) se añadieron cloruro de oxalilo (1,32 mL) y varias gotas de N,N-dimetilformamida y la mezcla se agitó a temperatura ambiente durante 5 h. La mezcla de reacción se concentró a

presión reducida y el residuo se lavó con éter diisopropílico para dar un sólido de color marrón pálido. A una solución (50 mL) del sólido obtenido en tetrahidrofurano se añadió una solución 1,1 M (12,0 mL) de hidruro de tri(isobutoxi)aluminio y litio en tetrahidrofurano a -78 °C y la mezcla se agitó a -78 °C durante 1,5 h, luego a 0 °C durante 3 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido de color marrón pálido. A una solución (40 mL) del sólido obtenido en tetrahidrofurano se añadió dióxido de manganeso activo (10,0 g) y la mezcla se agitó a 50 °C durante la noche. El dióxido de manganeso se filtró y el filtrado se concentró a presión reducida. El residuo se lavó con éter diisopropílico para dar el compuesto objeto del título (1,49 g, 63%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,65 (s, 3 H), 7,65 (d, J = 8,7 Hz, 1 H), 7,77 (dd, J = 8,7, 1,5 Hz, 1 H), 8,05 - 8,08 (m, 1 H), 10,08 (s, 1 H).

(5) 2-[ciclohexil(hidroxi)metil]-3-metil-1-benzofuran-5-carbonitrilo

A una solución (30 mL) de 2-formil-3-metil-1-benzofuran-5-carbonitrilo (1,49 g) sintetizada con anterioridad en tetrahidrofurano se añadió una solución 1,0 M (12,1 mL) de bromuro de ciclohexilmagnesio en tetrahidrofurano a 0 °C y la mezcla se agitó durante 1 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y

la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (25% de acetato de etilo/hexano) y luego se purificó por cromatografía en columna de gel de sílice NH (acetato de etilo) para dar el compuesto objeto del título (922 mg, 43%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 - 1,43 (m, 6 H), 1,48 - 1,99 (m, 5 H), 2,03 - 2,19 (m, 1 H), 2,24 (s, 3 H), 4,56 (dd, J = 8,4, 5,4 Hz, 1 H), 7,47 - 7,51 (m, 1 H), 7,52 - 7,57 (m, 1 H), 7,78 - 7,81 (m, 1 H).

(6) 2-[cloro(ciclohexil)metil]-3-metil-1-benzofuran-5-carbonitrilo

A una solución (10 mL) de 2-[ciclohexil(hidroxi)metil]-3-metil-1-benzofuran-5-carbonitrilo (922 mg) sintetizada con anterioridad en tolueno se añadió cloruro de tionilo (374 µL) y la mezcla se agitó a 100 °C durante 1 h. La mezcla de reacción se vertió en solución saturada acuosa de carbonato ácido de sodio helada y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (868 mg, 88%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 - 1,55 (m, 6 H), 1,62 - 1,74 (m, 2 H), 1,79 - 1,90 (m, 1 H), 2,10 - 2,22 (m, 1 H), 2,26 (s, 3 H), 2,28 - 2,39 (m, 1 H), 4,80 (d, J = 9,6 Hz, 1

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H), 7,51 - 7,55 (m, 1 H), 7,56 - 7,61 (m, 1 H), 7,81 - 7,83 (m, 1 H).

(7) ácido 4-{[(5-ciano-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}benzoico

A una mezcla de 2-[cloro(ciclohexil)metil]-3-metil-1-benzofuran-5-carbonitrilo (868 mg) sintetizado con anterioridad, 4-aminobenzoato de metilo (546 mg), yoduro de sodio (902 mg) y N,N-dimetilformamida (10 mL) se añadió carbonato de sodio (638 mg) y la mezcla se agitó a 80 °C durante la noche. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30% de acetato de etilo/hexano) para dar un sólido de color marrón pálido. A una mezcla del sólido obtenido, tetrahidrofurano (20 mL), agua (8 mL) y etanol (10 mL) se añadió solución acuosa 1 N de hidróxido de litio (3,38 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (40 mL) y ácido clorhídrico 1 N (3,50 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (621 mg, 53%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 1,41 (m, 5 H), 1,44 - 1,56 (m, 1 H), 1,62 - 2,01 (m, 4 H), 2,03 - 2,14 (m, 1 H), 2,28 (s, 3 H), 4,40 - 4,51 (m, 1 H), 4,52 - 4,67 (m, 1 H),

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6,56 (d, J = 8,8 Hz, 2 H), 7,41 - 7,46 (m, 1 H), 7,49 - 7,54 (m, 1 H), 7,75 - 7,77 (m, 1 H), 7,85 (d, J = 8,8 Hz, 2 H).

(8) 3-{[(4-{[(5-ciano-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[(5-ciano-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}benzoico (250 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (148 mg), monohidrato de 1-hidroxibenzotriazol (148 mg), trietilamina (269 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (185 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de hidrógeno-carbonato de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (50% de acetato de etilo/hexano) para dar el compuesto objeto del título (195 mg, 62%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,38 (m, 8 H), 1,45 - 1,63 (m, 3 H), 1,63 - 1,99 (m, 2 H), 2,03 - 2,15 (m, 1 H), 2,27 (s, 3 H), 2,54 - 2,61 (m, 2 H), 3,61 - 3,70 (m, 2 H), 4,14 (q, J = 7,2 Hz, 2 H), 4,39 - 4,46 (m, 1 H), 6,53 - 6,64 (m, 3 H), 7,41 - 7,45 (m, 1 H), 7,48 - 7,53 (m, 1 H), 7,55 (d, J = 8,7 Hz, 2 H), 7,76 (d, J = 1,5 Hz, 1 H).

(9) ácido 3-{[(4-{[(5-ciano-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico

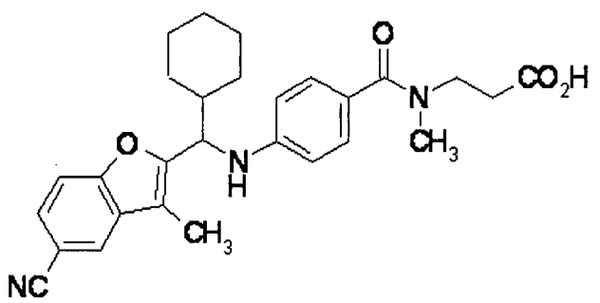
A una mezcla de 3-{[(4-{[(5-ciano-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoato de etilo (195 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de litio (800 µL) y la mezcla se agitó a temperatura ambiente durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (800 µL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (168 mg, 92%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,37 (m, 5 H), 1,43 - 1,54 (m, 1 H), 1,62 - 1,98 (m, 4 H), 2,03 - 2,14 (m, 1 H), 2,26 (s, 3 H), 2,57 - 2,67 (m, 2 H), 3,54 - 3,70 (m, 2 H), 4,42 (d, J = 8,1 Hz, 1 H), 6,51 - 6,65 (m, 3 H), 7,39 - 7,44 (m, 1 H), 7,45 - 7,56 (m, 3 H), 7,74 (d, J = 1,1 Hz, 1 H).

Ejemplo A99

Ácido 3-{[(4-{[(5-ciano-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico

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(1) 3-{[(4-{[(5-ciano-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[(5-ciano-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}benzoico (250 mg) sintetizado en el Ejemplo A98(7), 3-(metilamino)propanoato de etilo (127 mg), monohidrato de 1-hidroxibenzotriazol (148 mg), trietilamina (269 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (185 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (50% de acetato de etilo/hexano) para dar el compuesto objeto del título (193 mg, 60%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,38 (m, 8 H), 1,44 - 1,54 (m, 1 H), 1,62 - 1,98 (m, 4 H), 2,05 - 2,15 (m, 1 H),

2,27 (s, 3 H), 2,55 - 2,66 (m, 2 H), 3,00 (s, 3 H), 3,70 (t, J = 7,1 Hz, 2 H), 4,11 (q, J = 7,0 Hz, 2 H), 4,26 - 4,33 (m, 1 H), 4,40 (t, J = 7,9 Hz, 1 H), 6,55 (d, J = 8,6 Hz, 2 H), 7,21 (d, J = 8,6 Hz, 2 H), 7,40 - 7,46 (m, 1 H), 7,48 - 7,54 (m, 1 H), 7,76 (d, J = 1,5 Hz, 1 H).

(2) ácido 3-{[(4-{[(5-ciano-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico

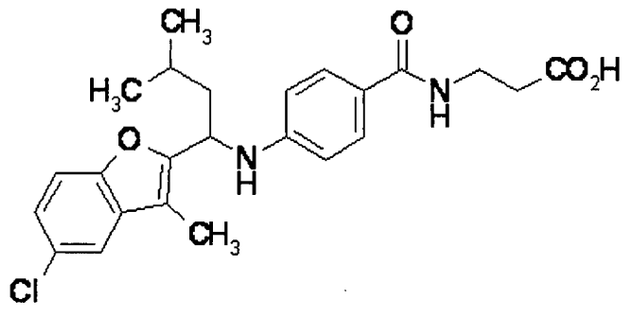
A una mezcla de 3-{[(4-{[(5-ciano-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (193 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de litio (770 µL) y la mezcla se agitó a temperatura ambiente durante 3 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (770 µL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (163 mg, 90%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,37 (m, 5 H), 1,44 - 1,54 (m, 1 H), 1,62 - 1,98 (m, 4 H), 2,04 - 2,15 (m, 1 H), 2,27 (s, 3 H), 2,61 - 2,70 (m, 2 H), 3,03 (s, 3 H), 3,69 (t, J = 6,5 Hz, 2 H), 4,40 (d, J = 7,9 Hz, 1 H), 6,55 (d, J = 8,9 Hz, 2 H), 7,24 (d, J = 8,9 Hz, 2 H), 7,40 - 7,46 (m, 1 H), 7,48 - 7,53 (m, 1 H), 7,76 (d, J = 1,1 Hz, 1 H).

Ejemplo A100

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Ácido 3-{[(4-{[1-(5-cloro-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil]amino}propanoico



(1)1-(5-cloro-3-metil-1-benzofuran-2-il)-3-metilbutan-1-ol

A una solución (20 mL) de 5-cloro-3-metil-1-benzofuran-2-carbaldehído (1,00 g) sintetizado en el Ejemplo A88(2) en tetrahidrofurano se añadió una solución 1,0 M (10,3 mL) de bromuro de isobutilmagnesio en tetrahidrofurano a 0 °C y la mezcla se agitó durante 1 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (20% de acetato de etilo/hexano) para dar el compuesto objeto del título (650 mg, 50%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 - 0,98 (m, 6 H), 1,53 - 1,70 (m, 1 H), 1,71 - 1,97 (m, 3 H), 2,22 (s, 3 H), 4,89 - 4,98 (m, 1 H), 7,19 - 7,23 (m, 1 H), 7,31 - 7,35 (m, 1 H), 7,43 (d, J = 2,2 Hz, 1 H).

(2)5-cloro-2-(1-cloro-3-metilbutil)-3-metil-1-benzofurano

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A una solución (10 mL) de 1-(5-cloro-3-metil-1-benzofuran-2-il)-3-metilbutan-1-ol (650 mg) sintetizado con anterioridad en tolueno se añadió cloruro de tionilo (225 µL) y la mezcla se agitó a 50 °C durante 2 h. La mezcla de reacción se vertió en solución saturada acuosa de carbonato ácido de sodio helada y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (668 mg, 96%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 (d, J = 2,5 Hz, 3 H), 0,95 (d, J = 2,7 Hz, 3 H), 1,58 - 1,74 (m, 1 H), 2,06 - 2,21 (m, 2 H), 2,23 (s, 3 H), 5,17 (t, J = 8,0 Hz, 1 H), 7,22 - 7,27 (m, 1 H), 7,34 - 7,38 (m, 1 H), 7,44 (d, J = 2,2 Hz, 1 H).

(3) ácido 4-{[1-(5-cloro-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}benzoico

A una mezcla de 5-cloro-2-(1-cloro-3-metilbutil)-3-metil-1-benzofurano (668 mg) sintetizado con anterioridad, 4-aminobenzoato de metilo (410 mg), yoduro de sodio (737 mg) y N,N-dimetilformamida (10 mL) se añadió carbonato de sodio (521 mg) y la mezcla se agitó a 80 °C durante 8 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (15% de acetato de etilo/hexano) para dar un aceite amarillo. A una mezcla del aceite obtenido, tetrahidrofurano (10 mL) y etanol (10 mL) se

añadió solución acuosa 1 N de hidróxido de sodio (10,0 mL) y la mezcla se agitó con calentamiento a reflujo durante 8 h y se concentró a presión reducida. El residuo se disolvió en agua (20 mL) y ácido clorhídrico 1 N (10,0 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (394 mg, 43%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 (d, J = 6,6 Hz, 3 H), 1,01 (d, J = 6,6 Hz, 3 H), 1,47 - 1,65 (m, 1 H), 1,87 (t, J = 7,4 Hz, 2 H), 2,27 (s, 3 H), 4,75 (t, J = 7,4 Hz, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 7,16 - 7,21 (m, 1 H), 7,27 - 7,31 (m, 1 H), 7,40 (d, J = 2,1 Hz, 1 H), 7,86 (d, J = 8,7 Hz, 2 H).

(4) 3-{[(4-{[1-(5-cloro-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[1-(5-cloro-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}benzoico (180 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (112 mg), monohidrato de 1-hidroxibenzotriazol (111 mg), trietilamina (202 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (139 mg) y la mezcla se agitó a temperatura ambiente durante 2,5 días. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de hidrógeno-carbonato de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (50% de acetato de

etilo/hexano) para dar el compuesto objeto del título (196 mg, 86%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,3 Hz, 3 H), 1,00 (d, J = 6,6 Hz, 3 H), 1,25 (t, J = 7,1 Hz, 3 H), 1,48 - 1,64 (m, 1 H), 1,85 (t, J = 7,3 Hz, 2 H), 2,25 (s, 3 H), 2,55 - 2,62 (m, 2 H), 3,61 - 3,69 (m, 2 H), 4,13 (q, J = 7,1 Hz, 2 H), 4,30 - 4,39 (m, 1 H), 4,65 - 4,76 (m, 1 H), 6,53 - 6,65 (m, 3 H), 7,13 - 7,19 (m, 1 H), 7,23 - 7,29 (m, 1 H), 7,38 (d, J = 2,2 Hz, 1 H), 7,55 (d, J = 8,8 Hz, 2 H).

(5) ácido 3-{[(4-{[1-(5-cloro-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil]amino}propanoico

A una mezcla de 3-{[(4-{[1-(5-cloro-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil]amino}propanoato de etilo (196 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,50 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,50 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (170 mg, 92%) en forma de un sólido blanco.

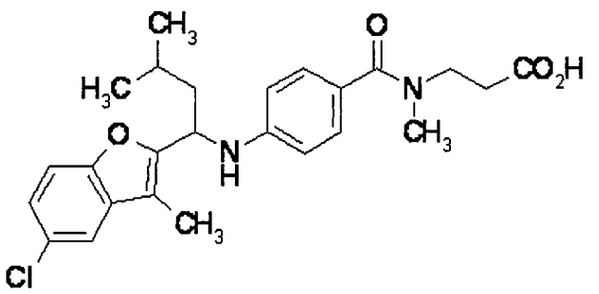
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,8 Hz, 3 H), 1,00 (d, J = 6,4 Hz, 3 H), 1,48 - 1,63 (m, 1 H), 1,85 (t, J = 7,5 Hz, 2 H), 2,24 (s, 3 H), 2,64 (t, J = 5,9 Hz, 2 H), 3,60 - 3,69 (m, 2 H), 4,70 (t, J = 7,5 Hz, 1 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,62 (t, J = 6,1 Hz, 1 H), 7,14 - 7,19 (m, 1 H),

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7,24 - 7,29 (m, 1 H), 7,38 (d, J = 1,9 Hz, 1 H), 7,54 (d, J = 8,7 Hz, 2 H).

Ejemplo A101

Ácido 3-{[(4-{[1-(5-cloro-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil](metil)amino}propanoico



(1) 3-{[(4-{[1-(5-cloro-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[1-(5-cloro-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}benzoico (180 mg) sintetizado en el Ejemplo A100(3), 3-(metilamino)propanoato de etilo (95,2 mg), monohidrato de 1-hidroxibenzotriazol (111 mg), trietilamina (202 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (139 mg) y la mezcla se agitó a temperatura ambiente durante 2,5 días. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por

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cromatografía en columna de gel de sílice (55% de acetato de etilo/hexano) para dar el compuesto objeto del título (199 mg, 85%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,6 Hz, 3 H), 1,00 (d, J = 6,6 Hz, 3 H), 1,23 (t, J = 7,1 Hz, 3 H), 1,49 - 1,64 (m, 1 H), 1,84 (t, J = 7,3 Hz, 2 H), 2,25 (s, 3 H), 2,56 - 2,67 (m, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,0 Hz, 2 H), 4,06 - 4,17 (m, 2 H), 4,19 - 4,29 (m, 1 H), 4,63 - 4,73 (m, 1 H), 6,56 (d, J = 8,5 Hz, 2 H), 7,14 - 7,19 (m, 1 H), 7,22 (d, J = 8,5 Hz, 2 H), 7,25 - 7,29 (m, 1 H), 7,38 (d, J = 2,2 Hz, 1 H).

(2) ácido 3-{[(4-{[1-(5-cloro-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil](metil)amino}propanoico

A una mezcla de 3-{[(4-{[1-(5-cloro-3-metil-1-benzofuran-2-il)-3-metilbutil]amino}fenil)carbonil](metil)amino}propanoato de etilo (199 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,50 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,50 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (174 mg, 93%) en forma de un sólido blanco.

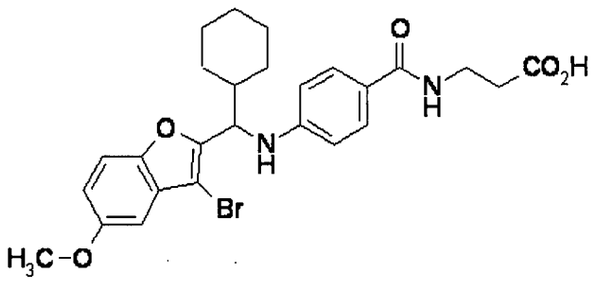
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 (d, J = 6,8 Hz, 3 H), 1,00 (d, J = 6,8 Hz, 3 H), 1,48 - 1,64 (m, 1 H), 1,85 (t, J = 7,2 Hz, 2 H), 2,25 (s, 3 H), 2,67 (t, J = 6,3 Hz, 2 H), 3,04 (s, 3 H), 3,71 (t, J = 6,3 Hz, 2 H), 4,69 (t, J = 7,6 Hz, 1 H),

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6,57 (d, J = 8,7 Hz, 2 H), 7,15 - 7,20 (m, 1 H), 7,22 - 7,31 (m, 3 H), 7,39 (d, J = 1,9 Hz, 1 H).

Ejemplo A102

Ácido 3-{[(4-{[(3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico



(1) N,5-dimetoxi-N-metil-1-benzofuran-2-carboxamida

A una solución (100 mL) de 2-hidroxi-5-metoxibenzaldehído (10,0 g) en N,N-dimetilformamida se añadieron 2-cloro-N-metoxi-N-metilacetamida (12,1 g), yoduro de sodio (24,0 g) y carbonato de potasio (22,1 g) y la mezcla se agitó a 50 °C durante la noche. La mezcla de reacción se enfrió hasta temperatura ambiente y el material insoluble se filtró. Al filtrado se añadió 1,8-diazabiciclo[5,4,0]undec-7-eno (9,82 mL) y la mezcla se agitó a 120 °C durante 2 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (40% de acetato de

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etilo/hexano) para dar el compuesto objeto del título (9,42 g, 61%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,42 (s, 3 H), 3,83 (s, 3 H), 3,85 (s, 3 H), 7,01 - 7,06 (m, 1 H), 7,07 - 7,09 (m, 1 H), 7,43 - 7,45 (m, 1 H), 7,46 - 7,51 (m, 1 H).

(2) 3-bromo-N,5-dimetoxi-N-metil-1-benzofuran-2-carboxamida

A una solución (100 mL) de N,5-dimetoxi-N-metil-1-benzofuran-2-carboxamida (9,24 g) sintetizado con anterioridad en ácido acético se añadió gota a gota bromo (2,21 mL) y la mezcla se agitó durante la noche a temperatura ambiente. El precipitado resultante se recogió por filtración y se lavó con éter diisopropílico para dar el compuesto objeto del título (9,48 g, 77%) en forma de un sólido anaranjado.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,43 (s, 3 H), 3,85 (s, 3 H), 3,95 (s, 3 H), 7,09 (d, J = 9,0 Hz, 1 H), 7,46 - 7,54 (m, 2 H).

(3)3-bromo-5-metoxi-1-benzofuran-2-carbaldehído

A una solución (40 mL) de 3-bromo-N,5-dimetoxi-N-metil-1-benzofuran-2-carboxamida (4,00 g) sintetizado con anterioridad en tetrahidrofurano se añadió hidruro de litio y aluminio (241 mg) a 0 °C y la mezcla se agitó durante 1 h. Se añadió adicionalmente hidruro de litio y aluminio (241 mg) y la mezcla se agitó a 0 °C durante 1 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por

cromatografía en columna de gel de sílice (20% de acetato de etilo/hexano) para dar el compuesto objeto del título (880 mg, 27%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,96 (s, 3 H), 7,17 (d, J = 9,1 Hz, 1 H), 7,48 - 7,53 (m, 1 H), 7,55 - 7,56 (m, 1 H), 9,85 (s, 1 H).

(4) (3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metanol

A una solución (50 mL) de 3-bromo-5-metoxi-1-benzofuran-2-carbaldehído (2,26 g) sintetizado con anterioridad en tetrahidrofurano se añadió una solución 1,0 M (13,3 mL) de bromuro de ciclohexilmagnesio en tetrahidrofurano a -78 °C y la mezcla se agitó a -78 °C durante 30 min, luego a 0 °C durante 1 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción, el tetrahidrofurano se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (20% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,82 g, 67%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,99 - 1,37 (m, 5 H), 1,49 - 1,60 (m, 1 H), 1,62 - 2,02 (m, 6 H), 3,93 (s, 3 H), 4,53 (t, J = 6,0 Hz, 1 H), 6,63 (s, 1 H), 6,89 (d, J = 8,8 Hz, 1 H), 7,34 (d, J = 8,8 Hz, 1 H).

(5) 3-bromo-2-[cloro(ciclohexil)metil]-5-metoxi-1-benzofurano

A una solución (20 mL) de (3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metanol (1,82 g) sintetizada con

anterioridad en tolueno se añadió cloruro de tionilo (469 µL) y la mezcla se agitó a 100 °C durante 1,5 h. La mezcla de reacción se vertió en solución saturada acuosa de carbonato ácido de sodio helada y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (1,73 g, 90%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,98 - 1,39 (m, 5 H), 1,51 - 1,87 (m, 4 H), 2,03 - 2,21 (m, 2 H), 3,92 (s, 3 H), 4,74 (d, J = 8,0 Hz, 1 H), 6,68 (s, 1 H), 6,92 (d, J = 8,8 Hz, 1 H), 7,36 (d, J = 8,8 Hz, 1 H).

(6) ácido 4-{[(3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}benzoico

A una mezcla de 3-bromo-2-[cloro(ciclohexil)metil]-5-metoxi-1-benzofurano (1,73 g) sintetizado con anterioridad, 4-aminobenzoato de metilo (878 mg), yoduro de sodio (1,45 g) y N,N-dimetilformamida (30 mL) se añadió carbonato de sodio (1,03 g) y la mezcla se agitó a 80 °C durante 8 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (25% de acetato de etilo/hexano) para dar un aceite amarillo. A una mezcla del aceite obtenido, tetrahidrofurano (10 mL) y etanol (10 mL) se añadió solución acuosa 1 N de hidróxido de sodio (10,0 mL) y la mezcla se agitó con calentamiento a reflujo durante 5 h y

se concentró a presión reducida. El residuo se disolvió en agua (20 mL) y ácido clorhídrico 1 N (10,0 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (318 mg, 14%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,04 - 1,37 (m, 5 H), 1,55 - 1,86 (m, 4 H), 1,87 - 2,02 (m, 2 H), 3,90 (s, 3 H), 4,44 (d, J = 6,6 Hz, 1 H), 6,56 (s, 1 H), 6,61 (d, J = 8,9 Hz, 2 H), 6,87 (d, J = 9,0 Hz, 1 H), 7,29 - 7,35 (m, 1 H), 7,87 (d, J = 8,9 Hz, 2 H).

(7) 3-{[(4-{[(3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[(3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}benzoico (125 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (63,0 mg), monohidrato de 1-hidroxibenzotriazol (62,9 mg), trietilamina (114 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (78,6 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (50% de acetato de

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etilo/hexano) para dar el compuesto objeto del título (134 mg, 88%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 - 1,37 (m, 8 H), 1,54 - 1,85 (m, 4 H), 1,87 - 1,99 (m, 2 H), 2,56 - 2,61 (m, 2 H), 3,62 - 3,70 (m, 2 H), 3,90 (s, 3 H), 4,14 (q, J = 7,1 Hz, 2 H), 4,36 - 4,41 (m, 2 H), 6,53 (d, J = 0,8 Hz, 1 H), 6,56 - 6,64 (m, 3 H), 6,86 (d, J = 8,8 Hz, 1 H), 7,29 (dd, J = 8,8, 0,8 Hz, 1 H), 7,56 (d, J = 8,8 Hz, 2 H).

(8) ácido 3-{[(4-{[(3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico

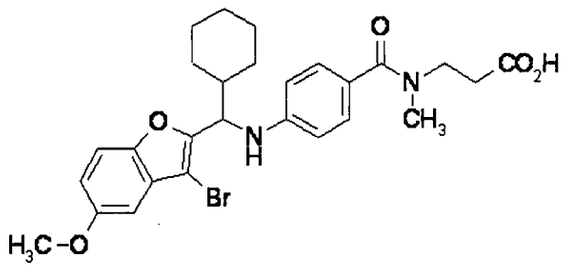
A una mezcla de 3-{[(4-{[(3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoato de etilo (134 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 2,5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (116 mg, 91%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,35 (m, 5 H), 1,53 - 1,84 (m, 4 H), 1,84 - 1,99 (m, 2 H), 2,61 (t, J = 5,7 Hz, 2 H), 3,59 - 3,68 (m, 2 H), 3,89 (s, 3 H), 4,38 (d, J = 6,4 Hz, 1 H), 6,52 - 6,66 (m, 4 H), 6,85 (d, J = 8,9 Hz, 1 H), 7,30 (dd, J = 8,9, 0,8 Hz, 1 H), 7,54 (d, J = 8,7 Hz, 2 H).

Ejemplo A103

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Ácido 3-{[(4-{[(3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) 3-{[(4-{[(3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[(3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}benzoico (125 mg) sintetizado en el Ejemplo A102(6), 3-(metilamino)propanoato de etilo (53,8 mg), monohidrato de 1-hidroxibenzotriazol (62,9 mg), trietilamina (114 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (78,6 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (35% de acetato de

1398

etilo/hexano) para dar el compuesto objeto del título (124 mg, 79%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,04 - 1,36 (m, 8 H), 1,55 - 1,85 (m, 4 H), 1,86 - 2,00 (m, 2 H), 2,62 (t, J = 7,0 Hz, 2 H), 3,02 (s, 3 H), 3,72 (t, J = 7,0 Hz, 2 H), 3,91 (s, 3 H), 4,12 (q, J = 7,1 Hz, 2 H), 4,24 - 4,41 (m, 2 H), 6,54 - 6,55 (m, 1 H), 6,58 (d, J = 8,8 Hz, 2 H), 6,86 (d, J = 8,8 Hz, 1 H), 7,24 (d, J = 8,8 Hz, 2 H), 7,30 (dd, J = 8,8, 0,8 Hz, 1 H).

(2) ácido 3-{[(4-{[(3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico

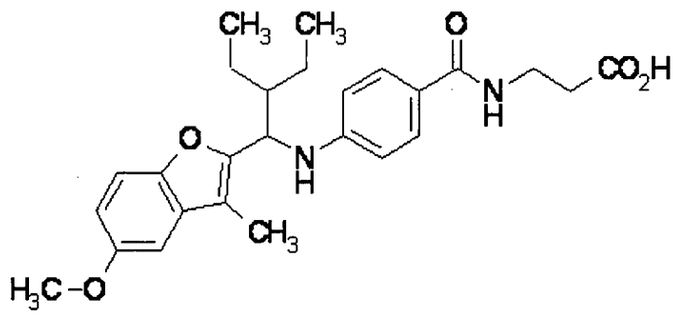
A una mezcla de 3-{[(4-{[(3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (124 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en etanol (5 mL), una solución acuosa 1 N de hidróxido de sodio (500 µL) se añadió y la mezcla se concentró a presión reducida. El residuo se disolvió en agua (5 mL) y ácido clorhídrico 1 N (500 µL) se añadió a 0 °C. El precipitado

1399

resultante se recogió por filtración para dar el compuesto objeto del título (107 mg, 91%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 - 1,36 (m, 5 H), 1,53 - 1,84 (m, 4 H), 1,85 - 2,00 (m, 2 H), 2,62 - 2,75 (m, 2 H), 3,05 (s, 3 H), 3,70 (t, J = 6,2 Hz, 2 H), 3,90 (s, 3 H), 4,37 (d, J = 6,4 Hz, 1 H), 6,55 (s, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 6,87 (d, J = 8,9 Hz, 1 H), 7,22 - 7,35 (m, 3 H).

Ejemplo A104

Ácido 3-{[(4-{[2-etil-1-(5-metoxi-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil]amino}propanoico




(1) ácido (2-acetil-4-metoxifenoxi)acético

A una mezcla de 1-(2-hidroxi-5-metoxifenil)etanona (25,0 g), bromoacetato de metilo (15,5 mL) y N,N-dimetilformamida (250 mL) se añadió carbonato de potasio (31,1 g) y la mezcla se agitó durante la noche a temperatura ambiente. El material insoluble se filtró, el ácido clorhídrico 1 N se añadió al filtrado y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un

1400

sólido marrón. A una mezcla del sólido obtenido, tetrahidrofurano (300 mL) y etanol (300 mL) se añadió solución acuosa 1 N de hidróxido de sodio (300 mL) y la mezcla se agitó durante la noche a temperatura ambiente y se concentró a presión reducida. Se añadió ácido clorhídrico 1 N (300 mL) se añadió al residuo a 0 °C y el precipitado resultante se recogió por filtración para dar el compuesto objeto del título (34,2 g, cuantitativo) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,67 (s, 3 H), 3,83 (s, 3 H), 4,72 (s, 2 H), 6,92 (d, J = 9,0 Hz, 1 H), 7,04 - 7,09 (m, 1 H), 7,29 (d, J = 3,0 Hz, 1 H).

(2) 5-metoxi-3-metil-1-benzofurano

Una mezcla de ácido (2-acetil-4-metoxifenoxi)acético (10,0 g) sintetizado con anterioridad, anhídrido acético (18,3 g) y ácido acético (100 mL) se agitó a 110 °C durante 5 h, se vertió en agua y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (5% de acetato de etilo/hexano) para dar el compuesto objeto del título (5,87 g, 81%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,21 (d, J = 1,1 Hz, 3 H), 3,86 (s, 3 H), 6,85 - 6,91 (m, 1 H), 6,95 (d, J = 2,7 Hz, 1 H), 7,33 (d, J = 8,8 Hz, 1 H), 7,35 - 7,39 (m, 1 H).

(3) 2-etil-1-(5-metoxi-3-metil-1-benzofuran-2-il)butan-1-ona

1401

A una mezcla de 5-metoxi-3-metil-1-benzofurano (2,00 g) sintetizado con anterioridad, cloruro de 2-etilbutanoilo (1,85 mL) y nitrometano (30 mL) se añadió cloruro de aluminio (3,28 g) y la mezcla se agitó a temperatura ambiente durante 1,5 h. Se añadió agua para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (6% de acetato de etilo/hexano) para dar el compuesto objeto del título (3,12 g, 97%) en forma de un aceite amarillo pálido. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 - 0,95 (m, 6 H), 1,52 - 1,66 (m, 2 H), 1,72 - 1,88 (m, 2 H), 2,59 (s, 3 H), 3,29 - 3,41 (m, 1 H), 3,88 (s, 3 H), 7,00 - 7,02 (m, 1 H), 7,06 - 7,11 (m, 1 H), 7,37 - 7,42 (m, 1 H).

(4) 4-{[2-etil-1-(5-metoxi-3-metil-1-benzofuran-2-il)butil]amino}benzoato de metilo

A una mezcla de 2-etil-1-(5-metoxi-3-metil-1-benzofuran-2-il)butan-1-ona (800 mg) sintetizada con anterioridad, 4-aminobenzoato de metilo (464 mg), trietilamina (3,43 mL) y cloruro de metileno (10 mL) se añadió cloruro de titanio (IV) (404 µL) y la mezcla se agitó durante la noche a temperatura ambiente bajo una atmósfera de argón. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción, el cloruro de metileno se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un

1402

aceite de color marrón oscuro. A una solución (20 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (882 µL) y cianoborohidruro de sodio (386 mg) y la mezcla se agitó a temperatura ambiente durante 1,5 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (20% de acetato de etilo/hexano) para dar el compuesto objeto del título (718 mg, 59%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 (t, J = 7,4 Hz, 3 H), 0,95 (t, J = 7,3 Hz, 3 H), 1,14 - 1,74 (m, 4 H), 1,81 - 1,95 (m, 1 H), 2,23 (s, 3 H), 3,81 (s, 3 H), 3,83 (s, 3 H), 4,47 - 4,53 (m, 1 H), 4,59 (t, J = 8,1 Hz, 1 H), 6,56 (d, J = 8,8 Hz, 2 H), 6,81 (dd, J = 8,8, 2,6 Hz, 1 H), 6,86 (d, J = 2,6 Hz, 1 H), 7,24 (d, J = 8,8 Hz, 1 H), 7,79 (d, J = 8,8 Hz, 2 H).

(5) ácido 4-{[2-etil-1-(5-metoxi-3-metil-1-benzofuran-2-il)butil]amino}benzoico

A una mezcla de 4-{[2-etil-1-(5-metoxi-3-metil-1-benzofuran-2-il)butil]amino}benzoato de metilo (718 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (5,00 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (5,00 mL) se añadió a 0 °C. El precipitado resultante se

recogió por filtración para dar el compuesto objeto del título (574 mg, 83%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 (t, J = 7,4 Hz, 3 H), 0,95 (t, J = 7,3 Hz, 3 H), 1,16 - 1,74 (m, 4 H), 1,82 - 1,95 (m, 1 H), 2,24 (s, 3 H), 3,83 (s, 3 H), 4,54 - 4,66 (m, 2 H), 6,58 (d, J = 8,8 Hz, 2 H), 6,83 (dd, J = 8,8, 2,6 Hz, 1 H), 6,88 (d, J = 2,6 Hz, 1 H), 7,25 (d, J = 8,8 Hz, 1 H), 7,85 (d, J = 8,8 Hz, 2 H).

(6) 3-{[(4-{[2-etil-1-(5-metoxi-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[2-etil-1-(5-metoxi-3-metil-1-benzofuran-2-il)butil]amino}benzoico (250 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (151 mg), monohidrato de 1-hidroxibenzotriazol (151 mg), trietilamina (275 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (188 mg) y la mezcla se agitó a temperatura ambiente durante 1 día. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (55% de acetato de etilo/hexano) para dar el compuesto objeto del título (85,0 mg, 27%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,87 (t, J = 7,4 Hz, 3 H), 0,95 (t, J = 7,4 Hz, 3 H), 1,24 (t, J = 7,1 Hz, 3 H), 1,30 - 1,74

1404

(m, 4 H), 1,81 - 1,93 (m, 1 H), 2,23 (s, 3 H), 2,54 - 2,62 (m, 2 H), 3,65 (q, J = 6,1 Hz, 2 H), 3,83 (s, 3 H), 4,13 (q, J = 7,1 Hz, 2 H), 4,40 (d, J = 8,8 Hz, 1 H), 4,52 - 4,60 (m, 1 H), 6,53 - 6,62 (m, 3 H), 6,78 - 6,84 (m, 1 H), 6,86 (d, J = 2,7 Hz, 1 H), 7,22 (s, 1 H), 7,54 (d, J = 8,8 Hz, 2 H).

(7) ácido 3-{[(4-{[2-etil-1-(5-metoxi-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil]amino}propanoico

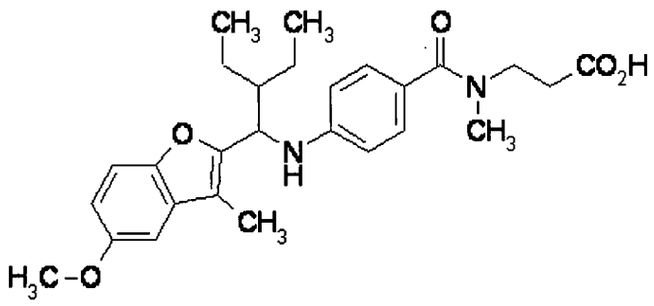
A una mezcla de 3-{[(4-{[2-etil-1-(5-metoxi-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil]amino}propanoato de etilo (85,0 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (75,4 mg, 94%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 (t, J = 7,3 Hz, 3 H), 0,94 (t, J = 7,3 Hz, 3 H), 1,14 - 1,72 (m, 4 H), 1,79 - 1,93 (m, 1 H), 2,22 (s, 3 H), 2,62 (t, J = 5,7 Hz, 2 H), 3,58 - 3,68 (m, 2 H), 3,82 (s, 3 H), 4,57 (d, J = 7,7 Hz, 1 H), 6,52 - 6,62 (m, 3 H), 6,81 (dd, J = 8,9, 2,5 Hz, 1 H), 6,86 (d, J = 2,5 Hz, 1 H), 7,24 (d, J = 8,9 Hz, 1 H), 7,52 (d, J = 8,9 Hz, 2 H).

Ejemplo A105

Ácido 3-{[(4-{[2-etil-1-(5-metoxi-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil](metil)amino}propanoico

1405



(1) 3-{[(4-{[2-etil-1-(5-metoxi-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[2-etil-1-(5-metoxi-3-metil-1-benzofuran-2-il)butil]amino}benzoico (250 mg) sintetizado en el Ejemplo A104(5), 3-(metilamino)propanoato de etilo (129 mg), monohidrato de 1-hidroxibenzotriazol (151 mg), trietilamina (275 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (188 mg) y la mezcla se agitó a temperatura ambiente durante 1 día. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de hidrógeno-carbonato de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (55% de acetato de etilo/hexano) para dar el compuesto objeto del título (261 mg, 81%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 (t, J = 7,4 Hz, 3 H), 0,94 (t, J = 7,4 Hz, 3 H), 1,23 (t, J = 7,1 Hz, 3 H), 1,29 - 1,73

1406

(m, 4 H), 1,79 - 1,93 (m, 1 H), 2,22 (s, 3 H), 2,61 (t, J = 7,1 Hz, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,1 Hz, 2 H), 3,83 (s, 3 H), 4,11 (q, J = 7,1 Hz, 2 H), 4,28 (d, J = 8,5 Hz, 1 H), 4,50 - 4,58 (m, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,79 - 6,83 (m, 1 H), 6,86 (d, J = 2,5 Hz, 1 H), 7,20 (d, J = 8,7 Hz, 2 H), 7,24 (d, J = 8,8 Hz, 1 H).

(2) ácido 3-{[(4-{[2-etil-1-(5-metoxi-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil](metil)amino}propanoico

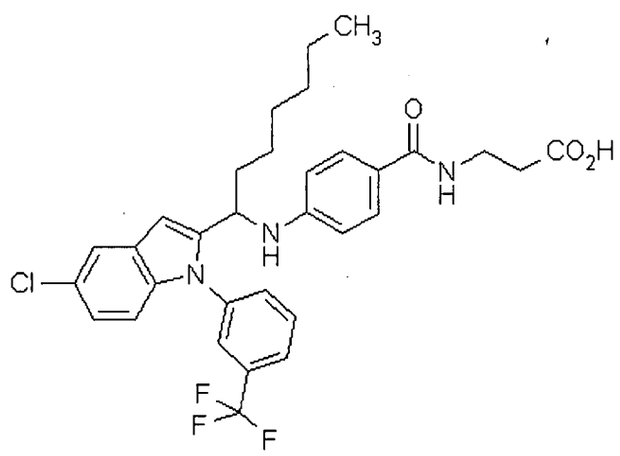
A una mezcla de 3-{[(4-{[2-etil-1-(5-metoxi-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil](metil)amino}propanoato de etilo (261 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (231 mg, 94%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 (t, J = 7,3 Hz, 3 H), 0,94 (t, J = 7,4 Hz, 3 H), 1,15 - 1,73 (m, 4 H), 1,80 - 1,93 (m, 1 H), 2,23 (s, 3 H), 2,65 (t, J = 6,6 Hz, 2 H), 3,03 (s, 3 H), 3,69 (t, J = 6,6 Hz, 2 H), 3,83 (s, 3 H), 4,55 (d, J = 7,7 Hz, 1 H), 6,56 (d, J = 8,9 Hz, 2 H), 6,82 (dd, J = 8,8, 2,4 Hz, 1 H), 6,87 (d, J = 2,4 Hz, 1 H), 7,20 - 7,28 (m, 3 H).

1407

Ejemplo A106

Ácido 3-[({4-[(1-{5-cloro-1-[3-(trifluorometil)fenil]-1H-indol-2-il}heptil)amino]fenil}carbonil)amino]propanoico



(1) 5-cloro-N-metoxi-N-metil-1H-indol-2-carboxamida

A una mezcla de ácido 5-cloro-1H-indol-2-carboxílico (15,0 g), clorhidrato de N,O-dimetilhidroxilamina (8,97 g), monohidrato de 1-hidroxibenzotriazol (14,1 g), trietilamina (25,6 mL) y N,N-dimetilformamida (200 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (17,6 g) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N para neutralizar la reacción, el precipitado resultante se recogió por filtración para dar el compuesto objeto del título (15,5 g, 84%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,43 (s, 3 H), 3,85 (s, 3 H), 7,14 - 7,18 (m, 1 H), 7,25 (dd, J = 8,7, 1,9 Hz, 1 H), 7,36

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(d, J = 8,7 Hz, 1 H), 7,66 (d, J = 1,9 Hz, 1 H), 9,32 (br s, 1 H).

(2) 1-(5-cloro-1H-indol-2-il)heptan-1-ona

A una solución (100 mL) de 5-cloro-N-metoxi-N-metil-1H-indol-2-carboxamida (9,14 g) sintetizada con anterioridad en tetrahidrofurano se añadió una solución 2,3 M (50,0 mL) de hexil-litio en hexano a -78 °C y la mezcla se agitó bajo una atmósfera de nitrógeno durante 1,5 h. Se añadió además una solución 2,3 M (38,3 mL) de hexil-litio en hexano y la mezcla se agitó a -78 °C durante 2 h. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con hexano para dar el compuesto objeto del título (6,90 g, 68%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 - 0,95 (m, 3 H), 1,26 - 1,48 (m, 6 H), 1,71 - 1,85 (m, 2 H), 2,92 (t, J = 7,7 Hz, 2 H), 7,11 - 7,14 (m, 1 H), 7,29 (dd, J = 8,8, 1,9 Hz, 1 H), 7,36 (d, J = 8,8 Hz, 1 H), 7,66 - 7,70 (m, 1 H), 9,05 - 9,19 (m, 1 H).

(3) 1-{5-cloro-1-[3-(trifluorometil)fenil]-1H-indol-2-il}heptan-1-ona

Una mezcla de 1-(5-cloro-1H-indol-2-il)heptan-1-one (9,14 g) sintetizado con anterioridad, 3-yodobenzotrifluoruro (1,97 mL), bromuro de cobre (I) (327 mg), carbonato de potasio (2,36 g) y N-metil-2-pirrolidona (30 mL) se

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desgasificó y la mezcla se agitó bajo una atmósfera de argón a 180 °C durante 1 día. Se añadió ácido clorhídrico 1 N a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (10% de acetato de etilo/hexano) para dar el compuesto objeto del título (0,78 g, 17%) en forma de un aceite marrón. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 - 0,92 (m, 3 H), 1,22 - 1,41 (m, 6 H), 1,62 - 1,74 (m, 2 H), 2,90 - 2,97 (m, 2 H), 6,95 (d, J = 8,8 Hz, 1 H), 7,25 (dd, J = 8,8, 1,9 Hz, 1 H), 7,35 (s, 1 H), 7,42 - 7,47 (m, 1 H), 7,49 - 7,53 (m, 1 H), 7,59 - 7,66 (m, 1 H), 7,69 - 7,74 (m, 2 H).

(4) 4-[(1-{5-cloro-1-[3-(trifluorometil)fenil]-1H-indol-2-il}heptil)amino]benzoato de metilo

A una mezcla de 1-{5-cloro-1-[3-(trifluorometil)fenil]-1H-indol-2-il}heptan-1-ona (709 mg) sintetizada con anterioridad, 4-aminobenzoato de metilo (263 mg), trietilamina (1,94 mL) y cloruro de metileno (10 mL) se añadió cloruro de titanio (IV) (229 µL) y la mezcla se agitó bajo una atmósfera de argón durante la noche a temperatura ambiente. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (10 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (498 µL) y

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cianoborohidruro de sodio (219 mg) y la mezcla se agitó a temperatura ambiente durante 1,5 h. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (15% de acetato de etilo/hexano) para dar el compuesto objeto del título (645 mg, 68%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 (t, J = 6,9 Hz, 3 H), 1,12 - 1,41 (m, 8 H), 1,74 - 1,93 (m, 2 H), 3,83 (s, 3 H), 4,03 - 4,15 (m, 1 H), 4,41 - 4,52 (m, 1 H), 6,33 (d, J = 8,8 Hz, 2 H), 6,57 (s, 1 H), 6,88 (d, J = 8,8 Hz, 1 H), 7,09 (dd, J = 8,8, 1,9 Hz, 1 H), 7,45 - 7,52 (m, 1 H), 7,54 - 7,65 (m, 3 H), 7,68 - 7,79 (m, 3 H).

(5) ácido 4-[(1-{5-cloro-1-[3-(trifluorometil)fenil]-1H-indol-2-il}heptil)amino]benzoico

A una mezcla de 4-[(1-{5-cloro-1-[3-(trifluorometil)fenil]-1H-indol-2-il}heptil)amino]benzoato de metilo (645 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (5,00 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (5,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar

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el compuesto objeto del título (589 mg, 94%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,80 (t, J = 6,8 Hz, 3 H), 1,03 - 1,34 (m, 6 H), 1,63 - 1,83 (m, 2 H), 4,29 - 4,44 (m, 1 H), 6,18 (d, J = 8,3 Hz, 2 H), 6,49 (s, 1 H), 6,82 (d, J = 8,5 Hz, 1 H), 7,02 (dd, J = 8,5, 1,9 Hz, 1 H), 7,34 - 7,56 (m, 4 H), 7,60 (d, J = 7,6 Hz, 1 H), 7,70 (d, J = 8,3 Hz, 2 H).

(6) 3-[({4-[(1-{5-cloro-1-[3-(trifluorometil)fenil]-1H-indol-2-il}heptil)amino]fenil}carbonil)amino]propanoato de etilo

A una mezcla de ácido 4-[(1-{5-cloro-1-[3-(trifluorometil)fenil]-1H-indol-2-il}heptil)amino]benzoico (250 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (109 mg), monohidrato de 1-hidroxibenzotriazol (109 mg), trietilamina (198 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (136 mg) y la mezcla se agitó a temperatura ambiente durante 3 días. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (50% de acetato de etilo/hexano) para dar el compuesto objeto del título (272 mg, 92%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,83 (t, J = 6,7 Hz, 3 H), 1,11 - 1,39 (m, 11 H), 1,75 - 1,90 (m, 2 H), 2,60 (t, J = 5,8 Hz, 2 H), 3,63 - 3,72 (m, 2 H), 3,93 - 4,04 (m, 1 H), 4,15 (q, J

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= 7,1 Hz, 2 H), 4,38 - 4,50 (m, 1 H), 6,35 (d, J = 8,5 Hz, 2 H), 6,53 - 6,64 (m, 2 H), 6,87 (d, J = 8,6 Hz, 1 H), 7,08 (dd, J = 8,6, 2,1 Hz, 1 H), 7,45 - 7,66 (m, 6 H), 7,70 (d, J = 7,1 Hz, 1 H).

(7) ácido 3-[({4-[(1-{5-cloro-1-[3-(trifluorometil)fenil]-1H-indol-2-il}heptil)amino]fenil}carbonil)amino]propanoico

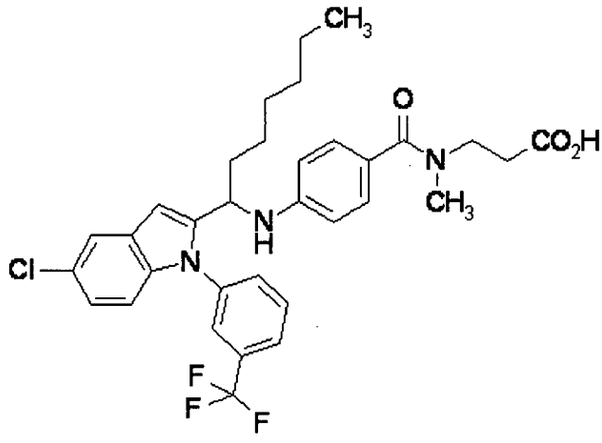
A una mezcla de 3-[({4-[(1-{5-cloro-1-[3-(trifluorometil)fenil]-1H-indol-2-il}heptil)amino]fenil}carbonil)amino]propanoato de etilo (273 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (5,00 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (5,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (253 mg, 97%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,78 (t, J = 6,8 Hz, 3 H), 1,01 - 1,32 (m, 8 H), 1,64 - 1,78 (m, 2 H), 2,30 - 2,43 (m, 2 H), 3,37 - 3,53 (m, 2 H), 4,29 - 4,43 (m, 1 H), 6,27 (d, J = 8,7 Hz, 2 H), 6,47 (s, 1 H), 6,76 - 6,89 (m, 2 H), 7,00 (dd, J = 8,7, 1,9 Hz, 1 H), 7,39 - 7,59 (m, 6 H), 7,63 (d, J = 7,6 Hz, 1 H).

Ejemplo A107

Ácido 3-[({4-[(1-{5-cloro-1-[3-(trifluorometil)fenil]-1H-indol-2-il}heptil)amino]fenil}carbonil)(metil)amino]propanoico

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(1) 3-[({4-[(1-{5-cloro-1-[3-(trifluorometil)fenil]-1H-indol-2-il}heptil)amino]fenil}carbonil)(metil)amino]propanoato de etilo

A una mezcla de ácido 4-[(1-{5-cloro-1-[3-(trifluorometil)fenil]-1H-indol-2-il}heptil)amino]benzoico (250 mg) sintetizado en el Ejemplo A106(5), 3-(metilamino)propanoato de etilo (93,1 mg), monohidrato de 1-hidroxibenzotriazol (109 mg), trietilamina (198 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (136 mg) y la mezcla se agitó a temperatura ambiente durante 3 días. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de hidrógeno-carbonato de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (40% de acetato de etilo/hexano) para dar el compuesto objeto del título (254 mg, 84%) en forma de un aceite amarillo pálido.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,83 (t, J = 6,9 Hz, 3 H), 1,11 - 1,37 (m, 11 H), 1,76 - 1,86 (m, 2 H), 2,62 (t, J = 7,3 Hz, 2 H), 3,02 (s, 3 H), 3,72 (t, J = 7,3 Hz, 2 H), 3,88 (d, J = 7,7 Hz, 1 H), 4,07 - 4,17 (m, 2 H), 4,35 - 4,46 (m, 1 H), 6,34 (d, J = 8,5 Hz, 2 H), 6,56 (s, 1 H), 6,88 (d, J = 8,8 Hz, 1 H), 7,08 (dd, J = 8,8, 2,0 Hz, 1 H), 7,17 (d, J = 8,5 Hz, 2 H), 7,51 (d, J = 7,7 Hz, 1 H), 7,56 (d, J = 2,0 Hz, 1 H), 7,57 - 7,66 (m, 2 H), 7,71 (d, J = 7,7 Hz, 1 H).

(2) ácido 3-[({4-[(1-{5-cloro-1-[3-(trifluorometil)fenil]-1H-indol-2-il}heptil)amino]fenil}carbonil)(metil)amino]propanoico

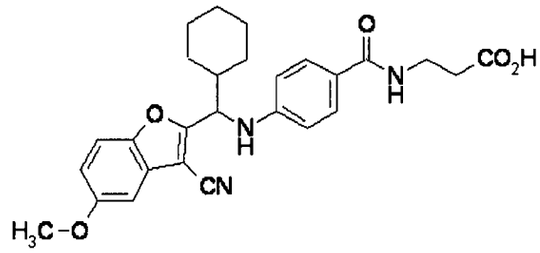
A una mezcla de 3-[({4-[(1-{5-cloro-1-[3-(trifluorometil)fenil]-1H-indol-2-il}heptil)amino]fenil}carbonil)(metil)amino]propanoato de etilo (254 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó durante la noche a temperatura ambiente y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (223 mg, 92%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,81 (t, J = 6,8 Hz, 3 H), 1,06 - 1,35 (m, 8 H), 1,70 - 1,82 (m, 2 H), 2,39 - 2,49 (m, 2 H), 2,92 (s, 3 H), 3,51 - 3,72 (m, 2 H), 4,38 (t, J = 6,8 Hz, 1 H), 6,32 (d, J = 8,5 Hz, 2 H), 6,53 (s, 1 H), 6,86 (d, J = 8,7 Hz, 1 H), 7,05 (dd, J = 8,7, 1,9 Hz, 1 H), 7,14 (d, J =

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8,5 Hz, 2 H), 7,47 - 7,55 (m, 2 H), 7,55 - 7,67 (m, 2 H), 7,70 (d, J = 7,6 Hz, 1 H).

Ejemplo A108

Ácido 3-{[(4-{[(3-ciano-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico




(1) (3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metanona

A una mezcla de dimetilsulfóxido (831 mL) y tetrahidrofurano (20 mL) se añadió anhídrido de ácido trifluoroacético (1,63 mL) a -78 °C y la mezcla se agitó durante 30 min y se añadió una solución (20 mL) de (3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metanol (2,03 g) sintetizada en el Ejemplo A102(4) en tetrahidrofurano. La mezcla de reacción se agitó bajo una atmósfera de argón a -78 °C durante 1 h, se añadió trietilamina (3,33 mL) y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (15% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,52 g, 75%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,20 - 1,63 (m, 5 H), 1,70 - 1,81 (m, 1 H), 1,82 - 2,00 (m, 4 H), 3,13 - 3,24 (m, 1 H),

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3,95 (s, 3 H), 7,12 (d, J = 9,3 Hz, 1 H), 7,46 - 7,50 (m, 2 H).

(2) 4-{[(3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}benzoato de metilo

A una mezcla de (3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metanona (1,52 g) sintetizada con anterioridad, 4-aminobenzoato de metilo (682 mg), trietilamina (5,03 mL) y cloruro de metileno (20 mL) se añadió cloruro de titanio (IV) (593 µL) y la mezcla se agitó bajo una atmósfera de argón durante la noche a temperatura ambiente. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (20 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (1,29 mL) y cianoborohidruro de sodio (567 mg) y la mezcla se agitó a temperatura ambiente durante 1,5 h. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción, el tetrahidrofurano se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (25% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,46 g, 69%) en forma de un sólido amarillo.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 - 1,38 (m, 5 H), 1,54 - 1,85 (m, 4 H), 1,85 - 2,01 (m, 2 H), 3,82 (s, 3 H), 3,90 (s, 3 H), 4,36 - 4,56 (m, 2 H), 6,54 (s, 1 H), 6,58 (d, J = 9,0 Hz, 2 H), 6,86 (d, J = 8,8 Hz, 1 H), 7,30 (d, J = 8,8 Hz, 1 H), 7,81 (d, J = 9,0 Hz, 2 H).

(3) ácido 4-{[(3-ciano-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}benzoico

A una mezcla de 4-{[(3-bromo-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}benzoato de metilo (1,46 g) sintetizado con anterioridad, cianuro de zinc (362 mg) y N,N-dimetilformamida (30 mL) se añadió tetrakis(trifenilfosfina)paladio (0) (357 mg) y después de desgasificar, la mezcla se agitó bajo una atmósfera de argón a 80 °C durante la noche. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (40% de acetato de etilo/hexano) para dar un sólido amarillo. A una solución (10 mL) del sólido obtenido en tetrahidrofurano se añadió solución acuosa 1 N de hidróxido de litio (2,88 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo. Etanol (10 mL) y agua (10 mL) se añadieron a la mezcla de reacción y la mezcla se agitó con calentamiento a reflujo durante 3 h. Se añadió adicionalmente una solución acuosa 1 N de hidróxido de litio (1,44 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua

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(20 mL) y ácido clorhídrico 1 N (4,35 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (547 mg, 94%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,05 - 1,38 (m, 5 H), 1,53 - 1,87 (m, 4 H), 1,87 - 2,01 (m, 2 H), 3,94 (s, 3 H), 4,42 - 4,60 (m, 2 H), 6,58 (d, J = 8,8 Hz, 2 H), 6,68 (d, J = 0,8 Hz, 1 H), 6,84 (d, J = 9,1 Hz, 1 H), 7,53 (dd, J = 9,1, 0,8 Hz, 1 H), 7,87 (d, J = 8,8 Hz, 2 H).

(4) 3-{[(4-{[(3-ciano-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[(3-ciano-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}benzoico (240 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (137 mg), monohidrato de 1-hidroxibenzotriazol (136 mg), trietilamina (248 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (171 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de hidrógeno-carbonato de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (60% de acetato de etilo/hexano) para dar el compuesto objeto del título (285 mg, 95%) en forma de un sólido amarillo.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,05 - 1,37 (m, 8 H), 1,53 - 1,86 (m, 4 H), 1,86 - 2,00 (m, 2 H), 2,59 (t, J = 6,3 Hz, 2 H), 3,62 - 3,70 (m, 2 H), 3,93 (s, 3 H), 4,14 (q, J = 7,1 Hz, 2 H), 4,35 - 4,45 (m, 2 H), 6,57 (d, J = 8,8 Hz, 2 H), 6,60 (t, J = 5,2 Hz, 1 H), 6,65 (d, J = 0,5 Hz, 1 H), 6,83 (d, J = 9,1 Hz, 1 H), 7,51 - 7,60 (m, 3 H).

(5) ácido 3-{[(4-{[(3-ciano-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico

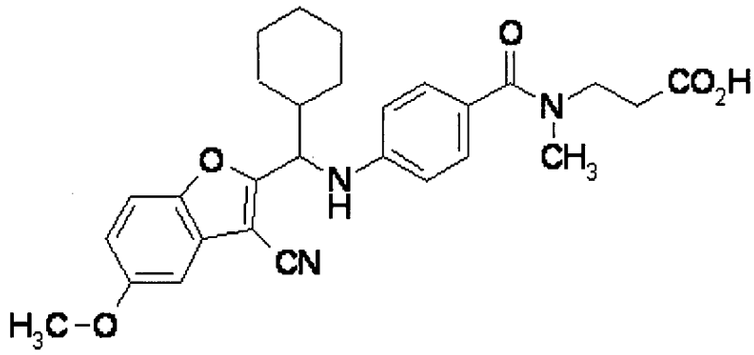
A una mezcla de 3-{[(4-{[(3-ciano-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoato de etilo (285 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (246 mg, 92%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,04 - 1,37 (m, 5 H), 1,50 - 1,63 (m, 1 H), 1,63 - 1,85 (m, 3 H), 1,85 - 2,01 (m, 2 H), 2,64 (t, J = 5,7 Hz, 2 H), 3,60 - 3,70 (m, 2 H), 3,93 (s, 3 H), 4,42 (d, J = 6,4 Hz, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 6,62 - 6,70 (m, 2 H), 6,83 (d, J = 9,2 Hz, 1 H), 7,50 - 7,59 (m, 3 H).

Ejemplo A109

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Ácido 3-{[(4-{[(3-ciano-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) 3-{[(4-{[(3-ciano-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[(3-ciano-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}benzoico (240 mg) sintetizado en el Ejemplo A108(3), 3-(metilamino)propanoato de etilo (117 mg), monohidrato de 1-hidroxibenzotriazol (136 mg), trietilamina (248 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (171 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por

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cromatografía en columna de gel de sílice (60% de acetato de etilo/hexano) para dar el compuesto objeto del título (253 mg, 82%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,04 - 1,36 (m, 8 H), 1,52 - 1,85 (m, 4 H), 1,85 - 1,99 (m, 2 H), 2,62 (t, J = 6,9 Hz, 2 H), 3,02 (s, 3 H), 3,71 (t, J = 6,9 Hz, 2 H), 3,94 (s, 3 H), 4,11 (q, J = 7,1 Hz, 2 H), 4,27 - 4,33 (m, 1 H), 4,35 - 4,43 (m, 1 H), 6,56 (d, J = 8,5 Hz, 2 H), 6,66 - 6,67 (m, 1 H), 6,83 (d, J = 9,1 Hz, 1 H), 7,23 (d, J = 8,5 Hz, 2 H), 7,52 (dd, J = 9,1, 0,8 Hz, 1 H).

(2) ácido 3-{[(4-{[(3-ciano-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico

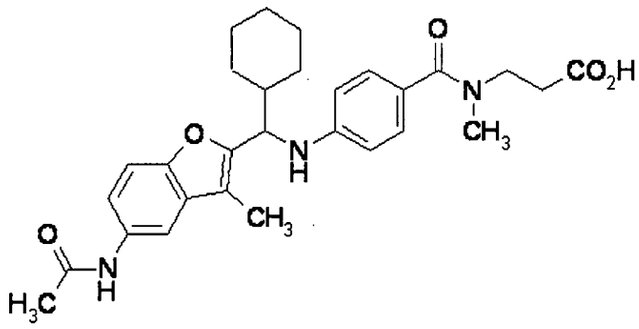
A una mezcla de 3-{[(4-{[(3-ciano-5-metoxi-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (253 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 3 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (218 mg, 91%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,04 - 1,36 (m, 5 H), 1,53 - 1,63 (m, 1 H), 1,63 - 1,84 (m, 3 H), 1,85 - 2,00 (m, 2 H), 2,61 - 2,73 (m, 2 H), 3,05 (s, 3 H), 3,71 (t, J = 6,6 Hz, 2

H), 3,94 (s, 3 H), 4,40 (d, J = 6,4 Hz, 1 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,67 (d, J = 0,8 Hz, 1 H), 6,84 (d, J = 9,1 Hz, 1 H), 7,26 (d, J = 8,7 Hz, 2 H), 7,55 (dd, J = 9,1, 0,8 Hz, 1 H).

Ejemplo A110

Ácido 3-[{[4-({[5-(acetilamino)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoico




(1) ciclohexil(3-metil-5-nitro-1-benzofuran-2-il)metanona

A una mezcla de 2'-hidroxi-5'-nitroacetofenona (5,00 g), 2-bromo-1-ciclohexiletanona (6,79 g) sintetizada en el Ejemplo A51(1) y N,N-dimetilformamida (50 mL) se añadió carbonato de potasio (7,63 g) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con éter diisopropílico para dar el compuesto objeto del título (4,18 g, 53%) en forma de un sólido amarillo.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,19 - 1,54 (m, 5 H), 1,70 - 1,81 (m, 1 H), 1,82 - 1,92 (m, 2 H), 1,92 - 2,02 (m, 2 H), 2,65 (s, 3 H), 3,24 - 3,36 (m, 1 H), 7,62 (d, J = 9,2 Hz, 1 H), 8,37 (dd, J = 9,2, 2,4 Hz, 1 H), 8,59 (d, J = 2,4 Hz, 1 H).

(2) 4-{[ciclohexil(3-metil-5-nitro-1-benzofuran-2-il)metil]amino}benzoato de metilo

A una mezcla de ciclohexil(3-metil-5-nitro-1-benzofuran-2-il)metanona (3,00 g) sintetizada con anterioridad, 4-aminobenzoato de metilo (1,57 g), trietilamina (11,6 mL) y cloruro de metileno (40 mL) se añadió cloruro de titanio (IV) (1,37 mL) y la mezcla se agitó durante la noche bajo una atmósfera de argón a temperatura ambiente. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (40 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (2,98 mL) y cianoborohidruro de sodio (1,31 g) y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (25% de acetato de

etilo/hexano) para dar el compuesto objeto del título (2,66 g, 61%) en forma de un sólido anaranjado.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 1,38 (m, 5 H), 1,45 - 1,59 (m, 1 H), 1,62 - 2,01 (m, 4 H), 2,05 - 2,15 (m, 1 H), 2,32 (s, 3 H), 3,81 (s, 3 H), 4,41 - 4,56 (m, 2 H), 6,55 (d, J = 9,1 Hz, 2 H), 7,43 (d, J = 8,9 Hz, 1 H), 7,80 (d, J = 9,1 Hz, 2 H), 8,16 (dd, J = 8,9, 2,4 Hz, 1 H), 8,36 (d, J = 2,4 Hz, 1 H).

(3) ácido 4-{[ciclohexil(3-metil-5-nitro-1-benzofuran-2-il)metil]amino}benzoico

A una mezcla de 4-{[ciclohexil(3-metil-5-nitro-1-benzofuran-2-il)metil]amino}benzoato de metilo (2,66 g) sintetizado con anterioridad, tetrahidrofurano (20 mL) y etanol (20 mL) se añadió solución acuosa 1 N de hidróxido de sodio (20,0 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (40 mL) y ácido clorhídrico 1 N (20,0 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración y el sólido obtenido se disolvió en acetato de etilo. La solución se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con éter diisopropílico para dar el compuesto objeto del título (2,22 g, 86%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 1,40 (m, 5 H), 1,45 - 1,58 (m, 1 H), 1,63 - 2,02 (m, 4 H), 2,04 - 2,16 (m, 1 H), 2,33 (s, 3 H), 4,48 (d, J = 8,0 Hz, 1 H), 6,57 (d, J = 9,1 Hz, 2 H), 7,43 (d, J = 8,9 Hz, 1 H), 7,86 (d, J = 9,1 Hz, 2

H), 8,17 (dd, J = 8,9, 2,4 Hz, 1 H), 8,37 (d, J = 2,4 Hz, 1 H).

(4) 3-{[(4-{[ciclohexil(3-metil-5-nitro-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclohexil(3-metil-5-nitro-1-benzofuran-2-il)metil]amino}benzoico (1,54 g) sintetizado con anterioridad, 3-(metilamino)propanoato de etilo (593 mg), monohidrato de 1-hidroxibenzotriazol (692 mg), trietilamina (1,26 mL) y N,N-dimetilformamida (15 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (867 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (50% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,41 g, 72%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 1,40 (m, 8 H), 1,44 - 1,56 (m, 1 H), 1,58 - 2,00 (m, 3 H), 2,06 - 2,17 (m, 1 H), 2,31 (s, 3 H), 2,61 (t, J = 7,0 Hz, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,0 Hz, 2 H), 4,06 - 4,16 (m, 2 H), 4,28 - 4,34 (m, 1 H), 4,42 (t, J = 8,0 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 7,22 (d, J = 8,7 Hz, 2 H), 7,43 (d, J = 9,1 Hz, 1 H), 8,16 (dd, J = 9,1, 2,5 Hz, 1 H), 8,35 - 8,37 (m, 1 H).

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(5) 3-{[(4-{[(5-amino-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una solución (20 mL) de 3-{[(4-{[ciclohexil(3-metil-5-nitro-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (600 mg) sintetizado con anterioridad en etanol se añadió óxido de platino (IV) (60,0 mg) y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 1 h. El óxido de platino se filtró y el filtrado se concentró para dar el compuesto objeto del título (579 mg, cuantitativo) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,35 (m, 8 H), 1,49 - 1,60 (m, 1 H), 1,60 - 1,95 (m, 4 H), 2,01 - 2,12 (m, 1 H), 2,17 (s, 3 H), 2,61 (t, J = 7,1 Hz, 2 H), 3,01 (s, 3 H), 3,56 (br s, 2 H), 3,70 (t, J = 7,1 Hz, 2 H), 4,11 (q, J = 7,1 Hz, 2 H), 4,30 - 4,34 (m, 2 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,59 (dd, J = 8,5, 2,5 Hz, 1 H), 6,69 (d, J = 2,5 Hz, 1 H), 7,14 (d, J = 8,5 Hz, 1 H), 7,20 (d, J = 8,7 Hz, 2 H).

(6) 3-[{[4-({[5-(acetilamino)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

A una solución (10 mL) de 3-{[(4-{[(5-amino-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (480 mg) sintetizado con anterioridad en tetrahidrofurano se añadieron trietilamina (204 µL) y anhídrido acético (138 µL) y la mezcla se agitó a temperatura

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ambiente durante 2,5 días. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (90% de acetato de etilo/hexano) para dar el compuesto objeto del título (366 mg, 70%) en forma de un aceite de color marrón pálido

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,38 (m, 8 H), 1,45 - 1,57 (m, 1 H), 1,60 - 1,97 (m, 4 H), 2,01 - 2,13 (m, 1 H), 2,17 (s, 3 H), 2,22 (s, 3 H), 2,61 (t, J = 7,1 Hz, 2 H), 3,01 (s, 3 H), 3,71 (t, J = 7,1 Hz, 2 H), 4,06 - 4,17 (m, 2 H), 4,31 - 4,41 (m, 2 H), 6,55 (d, J = 8,5 Hz, 2 H), 7,09 (dd, J = 8,8, 2,1 Hz, 1 H), 7,20 (d, J = 8,5 Hz, 2 H), 7,26 (d, J = 8,8 Hz, 1 H), 7,39 - 7,50 (m, 1 H), 7,71 (d, J = 2,1 Hz, 1 H).

(7) ácido 3-[{[4-({[5-(acetilamino)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoico

A una mezcla de 3-[{[4-({[5-(acetilamino)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (366 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de litio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 1 h. Adicionalmente se añadió solución acuosa de hidróxido de litio 1 N (1,00 mL) y

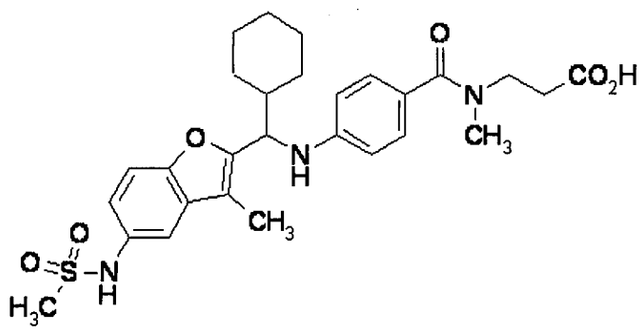
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la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (292 mg, 84%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,37 (m, 5 H), 1,45 - 1,57 (m, 1 H), 1,60 - 1,99 (m, 4 H), 2,04 - 2,25 (m, 7 H), 2,44 - 2,68 (m, 2 H), 2,99 (s, 3 H), 3,45 - 3,73 (m, 2 H), 4,35 (d, J = 7,9 Hz, 1 H), 6,54 (d, J = 8,7 Hz, 2 H), 7,03 - 7,11 (m, 1 H), 7,12 - 7,28 (m, 3 H), 7,57 - 7,68 (m, 2 H).

Ejemplo A111

Ácido 3-[({4-[(ciclohexil{3-metil-5-[(metilsulfonil)amino]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



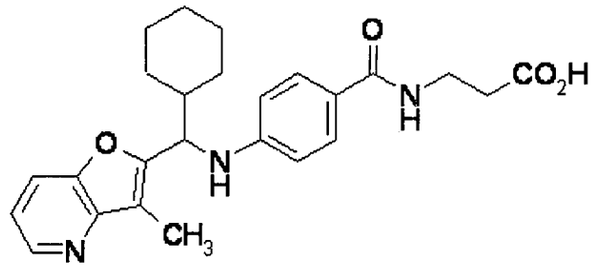
A una solución (10 mL) de 3-{[(4-{[(5-amino-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (412 mg) sintetizado en el Ejemplo A110(5) en

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N,N-dimetilacetamida se añadieron trietilamina (160 µL) y cloruro de metansulfonilo (89,0 µL) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (60% de acetato de etilo/hexano) para dar un aceite amarillo. A una mezcla del aceite obtenido, tetrahidrofurano (5 mL), etanol (5 mL) y agua (1 mL) se añadió solución acuosa de hidróxido de litio 4 N (500 µL) y la mezcla se agitó a temperatura ambiente durante 4 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (379 mg, 91%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,39 (m, 5 H), 1,45 - 1,57 (m, 1 H), 1,62 - 1,98 (m, 4 H), 2,06 - 2,15 (m, 1 H), 2,22 (s, 3 H), 2,64 (t, J = 6,2 Hz, 2 H), 2,93 (s, 3 H), 3,03 (s, 3 H), 3,68 (t, J = 6,2 Hz, 2 H), 4,37 (d, J = 8,0 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,65 - 6,71 (m, 1 H), 7,06 (dd, J = 8,6, 2,2 Hz, 1 H), 7,23 (d, J = 8,7 Hz, 2 H), 7,31 (d, J = 8,6 Hz, 1 H), 7,34 (d, J = 2,2 Hz, 1 H).

Ejemplo A112

Ácido 3-{[(4-{[ciclohexil(3-metilfuro[3,2-b]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoico



(1) ciclohexil(3-metilfuro[3,2-b]piridin-2-il)metanona

A una mezcla de 1-(3-hidroxipiridin-2-il)etanona (4,37 g), 2-bromo-1-ciclohexiletanona (9,82 g) sintetizada en el Ejemplo A51(1) y N,N-dimetilformamida (50 mL) se añadió carbonato de potasio (13,2 g) y la mezcla se agitó a temperatura ambiente durante 2,5 días. Se añadió ácido clorhídrico 1 N para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (20% de acetato de etilo/hexano) para dar el compuesto objeto del título (4,09 g, 53%) en forma de un sólido marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,19 - 1,59 (m, 5 H), 1,70 - 1,92 (m, 3 H), 1,92 - 2,03 (m, 2 H), 2,69 (s, 3 H), 3,26 - 3,39 (m, 1 H), 7,39 (dd, J = 8,3, 4,6 Hz, 1 H), 7,82 (dd, J = 8,3, 1,4 Hz, 1 H), 8,65 (dd, J = 4,6, 1,4 Hz, 1 H).

(2) 4-{[ciclohexil(3-metilfuro[3,2-b]piridin-2-il)metil]amino}benzoato de metilo

A una mezcla de ciclohexil(3-metilfuro[3,2-b]piridin-2-il)metanona (1,08 g) sintetizada con anterioridad, 4-

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aminobenzoato de metilo (738 mg), trietilamina (4,95 mL) y cloruro de metileno (20 mL) se añadió cloruro de titanio (IV) (584 µL) y la mezcla se agitó bajo una atmósfera de argón durante la noche a temperatura ambiente. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (20 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (1,27 mL) y cianoborohidruro de sodio (558 mg) y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción, el tetrahidrofurano se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (50% de acetato de etilo/hexano) para dar el compuesto objeto del título (789 mg, 47%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,99 - 1,38 (m, 5 H), 1,42 - 1,53 (m, 1 H), 1,64 - 2,01 (m, 4 H), 2,06 - 2,16 (m, 1 H), 2,77 (s, 3 H), 3,81 (s, 3 H), 4,50 - 4,63 (m, 2 H), 6,54 (d, J = 9,1 Hz, 2 H), 7,37 (dd, J = 8,2, 5,8 Hz, 1 H), 7,81 (d, J = 9,1 Hz, 2 H), 7,98 (dd, J = 8,2, 1,1 Hz, 1 H), 8,49 (dd, J = 5,8, 1,1 Hz, 1 H).

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(3) ácido 4-{[ciclohexil(3-metilfuro[3,2-b]piridin-2-il)metil]amino}benzoico

A una mezcla de 4-{[ciclohexil(3-metilfuro[3,2-b]piridin-2-il)metil]amino}benzoato de metilo (789 mg) sintetizado con anterioridad, tetrahidrofurano (10 mL) y etanol (10 mL) se añadió solución acuosa 1 N de hidróxido de sodio (10,0 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (20 mL) y ácido clorhídrico 1 N (10,0 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (718 mg, 94%) en forma de un sólido blanco.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 1,39 (m, 5 H), 1,47 - 1,60 (m, 1 H), 1,62 - 2,02 (m, 4 H), 2,03 - 2,17 (m, 1 H), 2,38 (s, 3 H), 4,47 - 4,72 (m, 2 H), 6,58 (d, J = 8,9 Hz, 2 H), 7,18 (dd, J = 8,3, 4,9 Hz, 1 H), 7,65 (dd, J = 8,3, 1,2 Hz, 1 H), 7,86 (d, J = 8,9 Hz, 2 H), 8,51 (dd, J = 4,9, 1,2 Hz, 1 H).

(4) 3-{[(4-{[ciclohexil(3-metilfuro[3,2-b]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclohexil(3-metilfuro[3,2-b]piridin-2-il)metil]amino}benzoico (330 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (209 mg), monohidrato de 1-hidroxibenzotriazol (208 mg), trietilamina (379 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (261 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución

acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (70% de acetato de etilo/hexano) para dar el compuesto objeto del título (383 mg, 91%) en forma de un aceite de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 1,38 (m, 8 H), 1,47 - 1,58 (m, 1 H), 1,61 - 2,00 (m, 4 H), 2,05 - 2,16 (m, 1 H), 2,35 (s, 3 H), 2,58 (t, J = 5,8 Hz, 2 H), 3,61 - 3,69 (m, 2 H), 4,13 (q, J = 7,1 Hz, 2 H), 4,42 - 4,52 (m, 2 H), 6,53 - 6,65 (m, 3 H), 7,13 (dd, J = 8,2, 4,7 Hz, 1 H), 7,54 (d, J = 8,8 Hz, 2 H), 7,58 - 7,62 (m, 1 H), 8,45 - 8,49 (m, 1 H).

(5) ácido 3-{[(4-{[ciclohexil(3-metilfuro[3,2-b]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoico

A una mezcla de 3-{[(4-{[ciclohexil(3-metilfuro[3,2-b]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo (383 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó durante la noche a temperatura ambiente y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (315 mg, 88%) en forma de un sólido blanco.

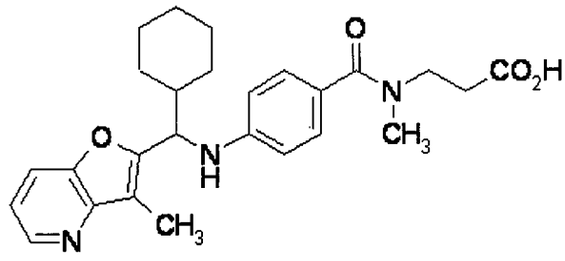
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 - 1,38 (m, 5 H), 1,44 - 1,57 (m, 1 H), 1,61 - 2,00 (m, 4 H), 2,05 - 2,18 (m, 1 H),

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2,35 (s, 3 H), 2,64 (t, J = 5,7 Hz, 2 H), 3,56 - 3,78 (m, 2 H), 4,46 (d, J = 8,0 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,72 (t, J = 6,1 Hz, 1 H), 7,18 (dd, J = 8,3, 4,9 Hz, 1 H), 7,54 (d, J = 8,7 Hz, 2 H), 7,66 (dd, J = 8,3, 1,3 Hz, 1 H), 8,49 (dd, J = 4,9, 1,3 Hz, 1 H).

Ejemplo A113

Ácido 3-{[(4-{[ciclohexil(3-metilfuro[3,2-b]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) 3-{[(4-{[ciclohexil(3-metilfuro[3,2-b]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclohexil(3-metilfuro[3,2-b]piridin-2-il)metil]amino}benzoico (330 mg) sintetizado en el Ejemplo A112(3), 3-(metilamino)propanoato de etilo (178 mg), monohidrato de 1-hidroxibenzotriazol (208 mg), trietilamina (379 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (261 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la

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reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (80% de acetato de etilo/hexano) para dar el compuesto objeto del título (292 mg, 67%) en forma de un aceite de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 - 1,38 (m, 8 H), 1,47 - 1,58 (m, 1 H), 1,61 - 2,00 (m, 4 H), 2,05 - 2,16 (m, 1 H), 2,35 (s, 3 H), 2,60 (t, J = 6,9 Hz, 2 H), 3,00 (s, 3 H), 3,69 (t, J = 6,9 Hz, 2 H), 4,10 (q, J = 7,0 Hz, 2 H), 4,35 (d, J = 8,3 Hz, 1 H), 4,45 (t, J = 8,3 Hz, 1 H), 6,56 (d, J = 8,5 Hz, 2 H), 7,13 (dd, J = 8,2, 4,9 Hz, 1 H), 7,20 (d, J = 8,5 Hz, 2 H), 7,60 (dd, J = 8,2, 1,4 Hz, 1 H), 8,47 (dd, J = 4,9, 1,4 Hz, 1 H).

(2) ácido 3-{[(4-{[ciclohexil(3-metilfuro[3,2-b]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

A una mezcla de 3-{[(4-{[ciclohexil(3-metilfuro[3,2-b]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (292 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y la mezcla se acidificó con ácido acético y se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida

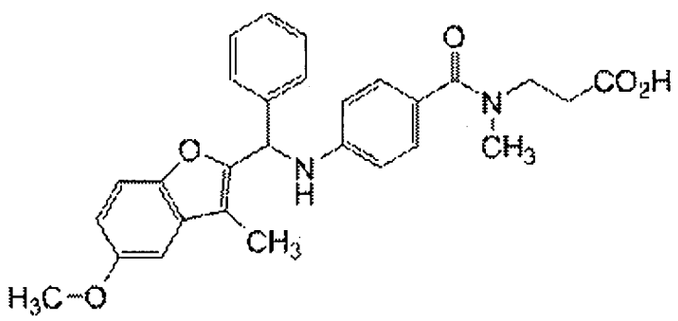
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para dar el compuesto objeto del título (278 mg, cuantitativo) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,39 (m, 5 H), 1,47 - 1,58 (m, 1 H), 1,61 - 2,00 (m, 4 H), 2,06 - 2,16 (m, 1 H), 2,34 (s, 3 H), 2,60 - 2,73 (m, 2 H), 3,03 (s, 3 H), 3,70 (t, J = 6,8 Hz, 2 H), 4,45 (d, J = 8,0 Hz, 1 H), 6,56 (d, J = 8,5 Hz, 2 H), 7,17 (dd, J = 8,2, 4,8 Hz, 1 H), 7,23 (d, J = 8,5 Hz, 2 H), 7,65 (dd, J = 8,2, 1,3 Hz, 1 H), 8,50 (dd, J = 4,8, 1,3 Hz, 1 H).

Ejemplo A114

Ácido 3-{[(4-{[(5-metoxi-3-metil-1-benzofuran-2-il)(fenil)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) (5-metoxi-3-metil-1-benzofuran-2-il)(fenil)metanona

A una mezcla de 5-metoxi-3-metil-1-benzofurano (2,00 g) sintetizado en el Ejemplo A104(2), cloruro de benzoilo (1,68 mL) y nitrometano (20 mL) se añadió cloruro de aluminio (3,28 g) y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió agua para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se

concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30% de acetato de etilo/hexano) y luego por cromatografía en columna de gel de sílice (20% de acetato de etilo/hexano) para dar el compuesto objeto del título (2,03 g, 62%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,62 (s, 3 H), 3,89 (s, 3 H), 7,05 (d, J = 2,5 Hz, 1 H), 7,10 (dd, J = 9,1, 2,5 Hz, 1 H), 7,42 (d, J = 9,1 Hz, 1 H), 7,47 - 7,63 (m, 3 H), 8,04 - 8,09 (m, 2 H).

(2) 4-{[(5-metoxi-3-metil-1-benzofuran-2-il)(fenil)metil]amino}benzoato de metilo

A una mezcla de (5-metoxi-3-metil-1-benzofuran-2-il)(fenil)metanona (2,03 g) sintetizada con anterioridad, 4-aminobenzoato de metilo (1,27 g), trietilamina (8,50 mL) y cloruro de metileno (30 mL) se añadió cloruro de titanio (IV) (1,00 mL) y la mezcla se agitó bajo una atmósfera de argón durante la noche a temperatura ambiente. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción, el cloruro de metileno se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (30 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (2,18 mL) y cianoborohidruro de sodio (955 mg) y la mezcla se agitó a temperatura ambiente durante 2,5 h. Se añadió solución saturada acuosa de carbonato ácido de sodio

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para neutralizar la reacción, el solvente orgánico se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30% de acetato de etilo/hexano) para dar el compuesto objeto del título (2,36 g, 77%) en forma de un sólido marrón. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,26 (s, 3 H), 3,82 (s, 3 H), 3,84 (s, 3 H), 4,98 (d, J = 6,0 Hz, 1 H), 5,82 (d, J = 6,0 Hz, 1 H), 6,60 (d, J = 8,7 Hz, 2 H), 6,84 (dd, J = 8,8, 2,6 Hz, 1 H), 6,90 (d, J = 2,6 Hz, 1 H), 7,23 - 7,37 (m, 4 H), 7,39 - 7,44 (m, 2 H), 7,82 (d, J = 8,7 Hz, 2 H).

(3) ácido 4-{[(5-metoxi-3-metil-1-benzofuran-2-il)(fenil)metil]amino}benzoico

A una mezcla de 4-{[(5-metoxi-3-metil-1-benzofuran-2-il)(fenil)metil]amino}benzoato de metilo (2,36 g) sintetizado con anterioridad, tetrahidrofurano (20 mL) y etanol (20 mL) se añadió solución acuosa 1 N de hidróxido de sodio (20,0 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (40 mL) y ácido clorhídrico 1 N (20,0 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración y el sólido obtenido se disolvió en acetato de etilo. La solución se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (1,09 g, 48%) en forma de un sólido de color rojo pálido.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,27 (s, 3 H), 3,84 (s, 3 H), 5,00 - 5,11 (m, 1 H), 5,84 (br s, 1 H), 6,61 (d, J = 8,8 Hz, 2 H), 6,81 - 6,88 (m, 1 H), 6,91 (d, J = 2,7 Hz, 1 H), 7,24 - 7,38 (m, 4 H), 7,39 - 7,45 (m, 2 H), 7,88 (d, J = 8,8 Hz, 2 H).

(4) 3-{[(4-{[(5-metoxi-3-metil-1-benzofuran-2-il)(fenil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[(5-metoxi-3-metil-1-benzofuran-2-il)(fenil)metil]amino}benzoico (400 mg) sintetizado con anterioridad, 3-(metilamino)propanoato de etilo (203 mg), monohidrato de 1-hidroxibenzotriazol (237 mg), trietilamina (431 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (297 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió agua para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (486 mg, 94%) en forma de un aceite de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,24 (t, J = 7,1 Hz, 3 H), 2,26 (s, 3 H), 2,56 - 2,67 (m, 2 H), 3,02 (s, 3 H), 3,71 (t, J = 7,1 Hz, 2 H), 3,84 (s, 3 H), 4,12 (q, J = 7,1 Hz, 2 H), 4,76 (d, J = 6,0 Hz, 1 H), 5,77 (d, J = 6,0 Hz, 1 H), 6,60 (d, J =

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8,5 Hz, 2 H), 6,84 (dd, J = 8,9, 2,6 Hz, 1 H), 6,90 (d, J = 2,6 Hz, 1 H), 7,20 - 7,37 (m, 6 H), 7,39 - 7,45 (m, 2 H).

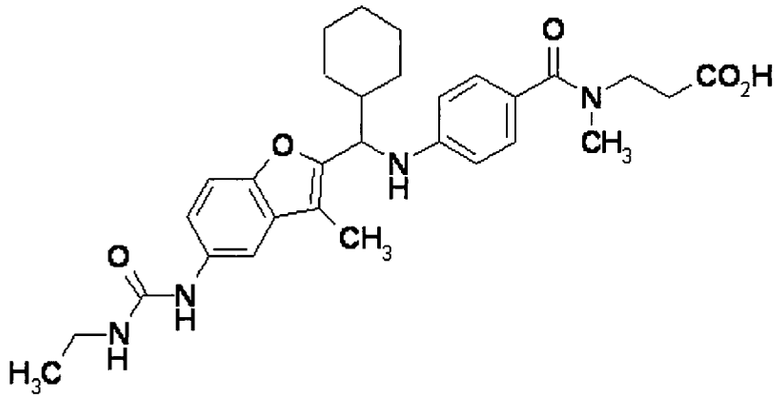
(5) ácido 3-{[(4-{[(5-metoxi-3-metil-1-benzofuran-2-il)(fenil)metil]amino}fenil)carbonil](metil)amino}propanoico

A una mezcla de 3-{[(4-{[(5-metoxi-3-metil-1-benzofuran-2-il)(fenil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (486 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 3 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (412 mg, 90%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,26 (s, 3 H), 2,68 (t, J = 6,4 Hz, 2 H), 3,05 (s, 3 H), 3,72 (t, J = 6,4 Hz, 2 H), 3,84 (s, 3 H), 5,78 (s, 1 H), 6,60 (d, J = 8,7 Hz, 2 H), 6,84 (dd, J = 8,9, 2,5 Hz, 1 H), 6,91 (d, J = 2,5 Hz, 1 H), 7,23 - 7,39 (m, 6 H), 7,39 - 7,47 (m, 2 H).

Ejemplo A115

Ácido 3-[({4-[(ciclohexil{5-[(etilcarbamoil)amino]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



(1) 3-[({4-[(ciclohexil{5-[(etilcarbamoil)amino]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo

A una solución (10 mL) de 3-{[(4-{[(5-amino-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (280 mg) sintetizado en el Ejemplo A110(5) en tetrahidrofurano se añadieron trietilamina (95 µL) e isocianato de etilo (54 µL) y la mezcla se agitó a temperatura ambiente durante 1 día. Trietilamina (95 µL) e isocianato de etilo (54 µL) se añadieron también y la mezcla se agitó durante la noche a temperatura ambiente. La mezcla de reacción se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (60 - 100% de acetato de etilo/hexano) para dar el compuesto objeto del título (304 mg, 95%) en forma de un aceite incoloro.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,37 (m, 11 H), 1,44 - 1,57 (m, 1 H), 1,59 - 1,96 (m, 4 H), 2,04 - 2,15 (m, 1 H), 2,19 (s, 3 H), 2,56 - 2,66 (m, 2 H), 3,02 (s, 3 H), 3,14 - 3,28 (m, 2 H), 3,71 (t, J = 7,0 Hz, 2 H), 4,11 (q, J = 7,1

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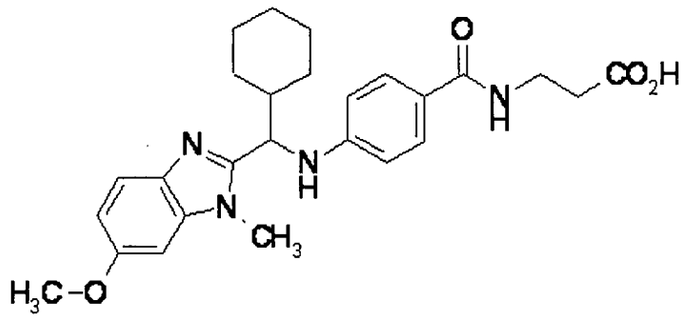
Hz, 2 H), 4,29 - 4,45 (m, 2 H), 6,55 (d, J = 8,8 Hz, 2 H), 6,72 - 6,83 (m, 1 H), 7,15 - 7,23 (m, 3 H), 7,43 - 7,48 (m, 1 H).

(2) ácido 3-[({4-[(ciclohexil{5-[(etilcarbamoil)amino]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

A una mezcla de 3-[({4-[(ciclohexil{5-[(etilcarbamoil)amino]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo (304 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de litio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (258 mg, 89%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,39 (m, 8 H), 1,45 - 1,57 (m, 1 H), 1,61 - 1,98 (m, 4 H), 2,06 - 2,20 (m, 4 H), 2,47 - 2,65 (m, 2 H), 2,99 (s, 3 H), 3,12 - 3,25 (m, 2 H), 3,52 - 3,70 (m, 2 H), 4,34 (d, J = 8,1 Hz, 1 H), 4,94 - 5,06 (m, 1 H), 6,53 (d, J = 8,7 Hz, 2 H), 6,88 (dd, J = 8,7, 2,0 Hz, 1 H), 7,14 - 7,24 (m, 3 H), 7,35 (d, J = 2,0 Hz, 1 H).

Ejemplo A116

Ácido 3-{[(4-{[ciclohexil(6-metoxi-1-metil-1H-bencimidazol-2-il)metil]amino}fenil)carbonil]amino}propanoico



(1) 5-metoxi-N-metil-2-nitroanilina

Una mezcla de ácido fórmico (7,64 g) y anhídrido acético (16,9 g) se agitó a 60 °C durante 2 h ten una solución (100 mL) de 5-metoxi-2-nitroanilina (9,30 g) en tetrahidrofurano se añadió gota a gota y la mezcla se agitó durante la noche a temperatura ambiente. La mezcla de reacción se concentró a presión reducida y el residuo se disolvió en acetato de etilo. La solución se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de sodio y se concentró a presión reducida. A una solución (200 mL) del residuo en tetrahidrofurano se añadió una solución 1,0 M (140 mL) de complejo de borano-tetrahidrofurano en tetrahidrofurano a 0 °C y la mezcla se agitó con calentamiento a reflujo durante 2 h. Metanol se añadió a la mezcla de reacción a 0 °C y la mezcla se agitó a temperatura ambiente durante 30 min. Tras agitar, ácido clorhídrico 1 N se añadió para ajustar a pH = 2. La mezcla de reacción se agitó con calentamiento a reflujo durante 1 h y se concentró a presión reducida y el residuo se disolvió en acetato de etilo. La solución se lavó con agua y salmuera

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saturada, se secó sobre sulfato de sodio y se concentró a presión reducida para dar el compuesto objeto del título (6,30 g, 62%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,01 (d, J = 5,1 Hz, 3H), 3,88 (s, 3H), 6,12 (d, J = 2,7 Hz, 1H), 6,24 (dd, J = 9,6, 2,4 Hz, 1H), 8,14 (d, J = 9,6 Hz, 1H), 8,29 (br, 1H).

(2) 6-metoxi-1-metil-1H-benzoimidazol

A una solución (200 mL) de 5-metoxi-N-metil-2-nitroanilina (6,30 g) sintetizada con anterioridad en metanol se añadió paladio/carbón al 10% (1,00 g) y la mezcla se agitó bajo una atmósfera de hidrógeno durante la noche a temperatura ambiente. El paladio/carbón se filtró y el filtrado se concentró. Una solución (150 mL) del residuo en ácido fórmico se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (25% de acetato de etilo/éter de petróleo) para dar el compuesto objeto del título (4,07 g, 60%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,78 (s, 3H), 3,87 (s, 3H), 6,81 (d, J = 2,4 Hz, 1H), 6,91 (dd, J = 8,7, 2,4 Hz, 1H), 7,66 (d, J = 9,0 Hz, 1H), 7,75 (s, 1H).

(3) N-metoxi-N-metilciclohexancarboxamida

Una mezcla de ácido ciclohexancarboxílico (6,10 g), clorhidrato de N,O-dimetilhidroxiamina (7,31 g), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (14,4 g), N,N-diisopropiletilamina (9,68 g), 4-dimetilaminopiridina (600 mg) y cloruro de metileno (150 mL) se agitó durante la noche a temperatura ambiente. Se añadió agua para neutralizar la

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reacción y la mezcla de reacción se extrajo con cloruro de metileno. El extracto se lavó con salmuera saturada, se secó sobre sulfato de sodio y se concentró a presión reducida para dar el compuesto objeto del título (7,57 g, 88%).

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,21-1,30 (m, 3H), 1,42-1,50 (m, 2H), 1,64-1,80 (m, 5H), 2,65 (m, 1H), 3,14 (s, 3H), 3,66 (s, 3H).

(4) ciclohexil(6-metoxi-1-metil-1H-bencimidazol-2-il)metanona

A una solución (100 mL) de 6-metoxi-1-metil-1H-benzoimidazol (4,07 g) sintetizada en el punto (2) antes mencionado en tetrahidrofurano se añadió una solución 1,6 M (30,1 mL) de n-butil-litio en hexano a -78 °C y la mezcla se agitó bajo una atmósfera de nitrógeno durante 30 min. Una solución (50 mL) de N-metoxi-N-metilciclohexancarboxamida (5,15 g) sintetizada en el punto (3) antes mencionado en tetrahidrofurano se añadió y la mezcla se agitó a -78 °C durante 1 h y a temperatura ambiente durante 2 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de sodio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/éter de petróleo = 1:5, relación en volumen) para dar el compuesto objeto del título (5,80 g, 85%) en forma de cristales blancos.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,23-1,33 (m, 1H), 1,45-1,52 (m, 4H), 1,64-1,72 (m, 1H), 1,78-1,86 (m, 2H), 1,96-2,01 (m, 2H), 3,82-3,90 (m, 1H), 3,91 (s, 3H), 4,09 (s, 3H), 6,77 (d, J =

2,4 Hz, 1H), 7,00 (dd, J = 9,0, 2,4 Hz, 1H), 7,76 (dd, J = 9,0, 2,4 Hz, 1H).

(5) 4-{[ciclohexil(6-metoxi-1-metil-1H-bencimidazol-2-il)metil]amino}benzoato de metilo

A una mezcla de ciclohexil(6-metoxi-1-metil-1H-bencimidazol-2-il)metanona (1,00 g) sintetizada con anterioridad, 4-aminobenzoato de metilo (611 mg), trietilamina (4,10 mL) y cloruro de metileno (20 mL) se añadió cloruro de titanio (IV) (482 µL) y la mezcla se agitó bajo una atmósfera de argón durante la noche a temperatura ambiente. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción, el cloruro de metileno se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido marrón oscuro. A una solución (20 mL) del sólido obtenido en tetrahidrofurano se añadieron ácido acético (1,05 mL) y cianoborohidruro de sodio (461 mg) y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción, el tetrahidrofurano se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (625 mg, 42%) en forma de un sólido de color marrón pálido.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,34 (m, 5 H), 1,46 - 1,58 (m, 1 H), 1,59 - 1,84 (m, 4 H), 1,95 - 2,11 (m, 1 H), 3,77 (s, 3 H), 3,82 (s, 3 H), 3,86 (s, 3 H), 4,59 (t, J = 8,0 Hz, 1 H), 5,04 (d, J = 8,0 Hz, 1 H), 6,63 (d, J = 8,8 Hz, 2 H), 6,76 (d, J = 2,4 Hz, 1 H), 6,88 (dd, J = 8,7, 2,4 Hz, 1 H), 7,59 (d, J = 8,7 Hz, 1 H), 7,80 (d, J = 8,8 Hz, 2 H).

(6) ácido 4-{[ciclohexil(6-metoxi-1-metil-1H-bencimidazol-2-il)metil]amino}benzoico

A una mezcla de 4-{[ciclohexil(6-metoxi-1-metil-1H-bencimidazol-2-il)metil]amino}benzoato de metilo (625 mg) sintetizado con anterioridad, tetrahidrofurano (10 mL) y etanol (10 mL) se añadió solución acuosa 1 N de hidróxido de sodio (5,00 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (20 mL) y ácido clorhídrico 1 N (5,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (600 mg, cuantitativo) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,01 - 1,36 (m, 5 H), 1,40 - 1,53 (m, 1 H), 1,56 - 1,86 (m, 3 H), 1,98 - 2,19 (m, 2 H), 3,83 (s, 3 H), 3,87 (s, 3 H), 4,59 - 4,69 (m, 1 H), 5,82 - 5,96 (m, 1 H), 6,68 (d, J = 8,9 Hz, 2 H), 6,78 (d, J = 2,3 Hz, 1 H), 6,91 (dd, J = 8,9, 2,3 Hz, 1 H), 7,64 (d, J = 8,9 Hz, 1 H), 7,88 (d, J = 8,9 Hz, 2 H).

(7) 3-{[(4-{[ciclohexil(6-metoxi-1-metil-1H-bencimidazol-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo

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A una mezcla de ácido 4-{[ciclohexil(6-metoxi-1-metil-1H-bencimidazol-2-il)metil]amino}benzoico (270 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (158 mg), monohidrato de 1-hidroxibenzotriazol (158 mg), trietilamina (287 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (198 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con ácido clorhídrico 1 N, solución saturada acuosa de hidrógeno-carbonato de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (60 - 100% de acetato de etilo/hexano) para dar el compuesto objeto del título (151 mg, 45%) en forma de un aceite amarillo pálido. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 - 1,35 (m, 8 H), 1,45 - 1,55 (m, 1 H), 1,58 - 1,85 (m, 3 H), 1,94 - 2,11 (m, 2 H), 2,58 (t, J = 6,1 Hz, 2 H), 3,66 (q, J = 6,1 Hz, 2 H), 3,76 (s, 3 H), 3,86 (s, 3 H), 4,14 (q, J = 7,1 Hz, 2 H), 4,56 (t, J = 7,8 Hz, 1 H), 4,90 (d, J = 7,8 Hz, 1 H), 6,58 - 6,67 (m, 3 H), 6,75 (d, J = 2,5 Hz, 1 H), 6,88 (dd, J = 8,8, 2,5 Hz, 1 H), 7,55 (d, J = 8,8 Hz, 2 H), 7,58 (d, J = 8,8 Hz, 1 H).

(8) ácido 3-{[(4-{[ciclohexil(6-metoxi-1-metil-1H-bencimidazol-2-il)metil]amino}fenil)carbonil]amino}propanoico

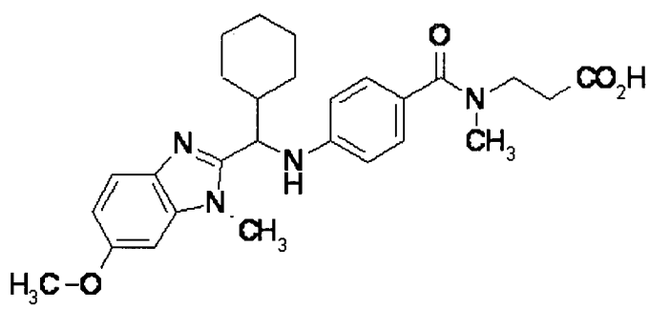
A una mezcla de 3-{[(4-{[ciclohexil(6-metoxi-1-metil-1H-bencimidazol-2-il)metil]amino}fenil)carbonil]amino}propanoato

de etilo (151 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 2,5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (124 mg, 87%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 1,30 (m, 5 H), 1,30 - 1,40 (m, 1 H), 1,60 - 1,70 (m, 2 H), 1,71 - 1,83 (m, 1 H), 1,90 - 2,05 (m, 1 H), 2,12 - 2,23 (m, 1 H), 2,71 (t, J = 5,4 Hz, 2 H), 3,72 - 3,84 (m, 2 H), 3,86 (s, 3 H), 3,87 (s, 3 H), 4,57 - 4,66 (m, 1 H), 6,74 (d, J = 8,9 Hz, 2 H), 6,78 (d, J = 2,4 Hz, 1 H), 6,90 (dd, J = 8,9, 2,4 Hz, 1 H), 7,24 - 7,32 (m, 1 H), 7,52 (d, J = 8,9 Hz, 1 H), 7,66 (d, J = 8,9 Hz, 2 H).

Ejemplo A117

Ácido 3-{[(4-{[ciclohexil(6-metoxi-1-metil-1H-bencimidazol-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico



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(1) 3-{[(4-{[ciclohexil(6-metoxi-1-metil-1H-bencimidazol-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclohexil(6-metoxi-1-metil-1H-bencimidazol-2-il)metil]amino}benzoico (270 mg) sintetizado en el Ejemplo A116(6), 3-(metilamino)propanoato de etilo (135 mg), monohidrato de 1-hidroxibenzotriazol (158 mg), trietilamina (287 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (198 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con ácido clorhídrico 1 N, solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (60 - 100% de acetato de etilo/hexano) para dar el compuesto objeto del título (103 mg, 30%) en forma de un aceite amarillo pálido. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,33 (m, 8 H), 1,45 - 1,55 (m, 1 H), 1,59 - 1,92 (m, 3 H), 1,92 - 2,13 (m, 2 H), 2,61 (t, J = 7,0 Hz, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,0 Hz, 2 H), 3,76 (s, 3 H), 3,86 (s, 3 H), 4,11 (q, J = 7,1 Hz, 2 H), 4,49 - 4,57 (m, 1 H), 4,75 (d, J = 8,2 Hz, 1 H), 6,63 (d, J = 8,5 Hz, 2 H), 6,76 (d, J = 2,4 Hz, 1 H), 6,88 (dd, J

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= 8,8, 2,4 Hz, 1 H), 7,22 (d, J = 8,5 Hz, 2 H), 7,59 (d, J = 8,8 Hz, 1 H).

(2) ácido 3-{[(4-{[ciclohexil(6-metoxi-1-metil-1H-bencimidazol-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

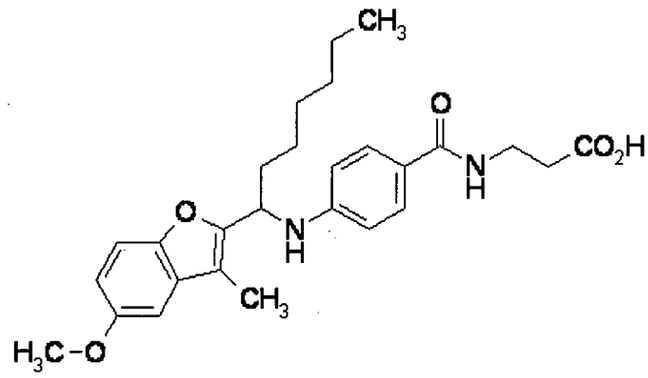
A una mezcla de 3-{[(4-{[ciclohexil(6-metoxi-1-metil-1H-bencimidazol-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (103 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (72,1 mg, 74%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 1,30 (m, 5 H), 1,31 - 1,41 (m, 1 H), 1,57 - 1,81 (m, 3 H), 1,88 - 2,03 (m, 1 H), 2,07 - 2,19 (m, 1 H), 2,69 - 2,81 (m, 2 H), 3,10 (s, 3 H), 3,73 - 3,82 (m, 2 H), 3,84 (s, 3 H), 3,85 (s, 3 H), 4,54 (d, J = 8,1 Hz, 1 H), 6,59 (d, J = 8,5 Hz, 2 H), 6,77 (d, J = 2,4 Hz, 1 H), 6,88 (dd, J = 8,9, 2,4 Hz, 1 H), 7,20 - 7,28 (m, 2 H), 7,54 (d, J = 8,9 Hz, 1 H).

Ejemplo A118

Ácido 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)heptil]amino}fenil)carbonil]amino}propanoico

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(1) 1-(5-metoxi-3-metil-1-benzofuran-2-il)heptan-1-ona

A una mezcla de 5-metoxi-3-metil-1-benzofurano (1,87 g) sintetizado en el Ejemplo A104(2), cloruro de heptanoilo (2,14 mL) y nitrometano (20 mL) se añadió cloruro de aluminio (3,07 g) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió agua para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (7% de acetato de etilo/hexano) para dar el compuesto objeto del título (2,34 g, 74%) en forma de un sólido amarillo pálido. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 - 0,95 (m, 3 H), 1,24 - 1,48 (m, 6 H), 1,67 - 1,82 (m, 2 H), 2,57 (s, 3 H), 2,96 (t, J = 7,4 Hz, 2 H), 3,87 (s, 3 H), 7,00 (d, J = 2,6 Hz, 1 H), 7,07 (dd, J = 9,1, 2,6 Hz, 1 H), 7,38 (d, J = 9,1 Hz, 1 H).

(2) 4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)heptil]amino}benzoato de metilo

A una mezcla de 1-(5-metoxi-3-metil-1-benzofuran-2-il)heptan-1-ona (1,18 g) sintetizada con anterioridad, 4-aminobenzoato de metilo (715 mg), trietilamina (4,79 mL) y

cloruro de metileno (20 mL) se añadió cloruro de titanio (IV) (566 µL) y la mezcla se agitó bajo una atmósfera de argón durante la noche a temperatura ambiente. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción, el cloruro de metileno se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (20 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (1,23 mL) y cianoborohidruro de sodio (540 mg) y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 20% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,17 g, 66%) en forma de un aceite de color marrón pálido

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,82 - 0,88 (m, 3 H), 1,18 - 1,40 (m, 8 H), 1,88 - 2,03 (m, 2 H), 2,24 (s, 3 H), 3,81 (s, 3 H), 3,83 (s, 3 H), 4,51 (d, J = 7,7 Hz, 1 H), 4,58 - 4,68 (m, 1 H), 6,56 (d, J = 8,8 Hz, 2 H), 6,82 (dd, J = 8,8, 2,5 Hz, 1 H), 6,87 (d, J = 2,5 Hz, 1 H), 7,25 (d, J = 8,8 Hz, 1 H), 7,80 (d, J = 8,8 Hz, 2 H).

(3) ácido 4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)heptil]amino}benzoico

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A una mezcla de 4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)heptil]amino}benzoato de metilo (1,17 g) sintetizado con anterioridad, tetrahidrofurano (20 mL) y etanol (20 mL) se añadió solución acuosa 1 N de hidróxido de sodio (20,0 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (20 mL) y ácido clorhídrico 1 N (20,0 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (1,02 g, 90%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,80 - 0,92 (m, 3 H), 1,16 - 1,44 (m, 8 H), 1,90 - 2,03 (m, 2 H), 2,25 (s, 3 H), 3,84 (s, 3 H), 4,65 (t, J = 7,3 Hz, 1 H), 6,58 (d, J = 8,8 Hz, 2 H), 6,84 (dd, J = 8,9, 2,5 Hz, 1 H), 6,89 (d, J = 2,5 Hz, 1 H), 7,26 (d, J = 8,9 Hz, 1 H), 7,87 (d, J = 8,8 Hz, 2 H).

(4) 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)heptil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)heptil]amino}benzoico (300 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (175 mg), monohidrato de 1-hidroxibenzotriazol (175 mg), trietilamina (318 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (219 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de

carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 100% de acetato de etilo/hexano) para dar el compuesto objeto del título (320 mg, 85%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,81 - 0,90 (m, 3 H), 1,17 - 1,44 (m, 11 H), 1,89 - 2,00 (m, 2 H), 2,24 (s, 3 H), 2,58 (t, J = 6,0 Hz, 2 H), 3,66 (q, J = 6,0 Hz, 2 H), 3,83 (s, 3 H), 4,14 (q, J = 7,1 Hz, 2 H), 4,37 - 4,44 (m, 1 H), 4,55 - 4,66 (m, 1 H), 6,53 - 6,64 (m, 3 H), 6,82 (dd, J = 8,8, 2,4 Hz, 1 H), 6,87 (d, J = 2,4 Hz, 1 H), 7,24 (d, J = 8,8 Hz, 1 H), 7,55 (d, J = 8,8 Hz, 2 H).

(5) ácido 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)heptil]amino}fenil)carbonil]amino}propanoico

A una mezcla de 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)heptil]amino}fenil)carbonil]amino}propanoato de etilo (320 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 3 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (213 mg, 71%) en forma de un sólido de color marrón pálido.

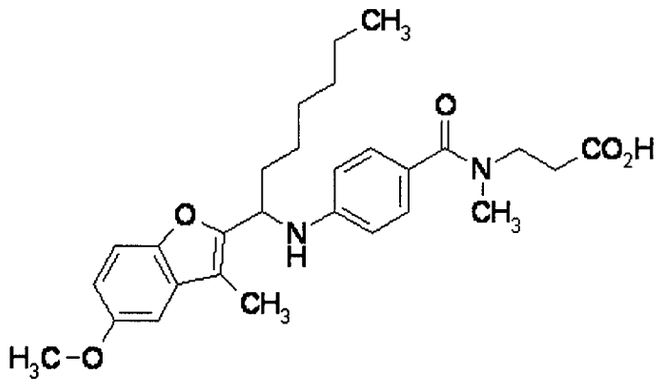
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 (t, J = 6,8 Hz, 3 H), 1,16 - 1,43 (m, 8 H), 1,85 - 2,03 (m, 2 H), 2,23 (s, 3 H), 2,63

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(t, J = 5,8 Hz, 2 H), 3,59 - 3,69 (m, 2 H), 3,83 (s, 3 H), 4,60 (t, J = 7,3 Hz, 1 H), 6,56 (d, J = 8,9 Hz, 2 H), 6,64 (t, J = 6,1 Hz, 1 H), 6,82 (dd, J = 8,9, 2,5 Hz, 1 H), 6,88 (d, J = 2,5 Hz, 1 H), 7,23 - 7,27 (m, 1 H), 7,53 (d, J = 8,9 Hz, 2 H).

Ejemplo A119

Ácido 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)heptil]amino}fenil)carbonil](metil)amino}propanoico




(1) 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)heptil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)heptil]amino}benzoico (300 mg) sintetizado en el Ejemplo A118(3), 3-(metilamino)propanoato de etilo (150 mg), monohidrato de 1-hidroxibenzotriazol (175 mg), trietilamina (318 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (219 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución

acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (289 mg, 75%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 (t, J = 6,9 Hz, 3 H), 1,17 - 1,45 (m, 11 H), 1,88 - 2,01 (m, 2 H), 2,24 (s, 3 H), 2,61 (t, J = 7,0 Hz, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,0 Hz, 2 H), 3,84 (s, 3 H), 4,11 (q, J = 7,1 Hz, 2 H), 4,23 - 4,37 (m, 1 H), 4,54 - 4,63 (m, 1 H), 6,56 (d, J = 8,8 Hz, 2 H), 6,82 (dd, J = 8,8, 2,4 Hz, 1 H), 6,88 (d, J = 2,4 Hz, 1 H), 7,22 (d, J = 8,8 Hz, 2 H), 7,25 (d, J = 8,8 Hz, 1 H).

(2) ácido 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)heptil]amino}fenil)carbonil](metil)amino}propanoico

A una mezcla de 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)heptil]amino}fenil)carbonil](metil)amino}propanoato de etilo (289 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto

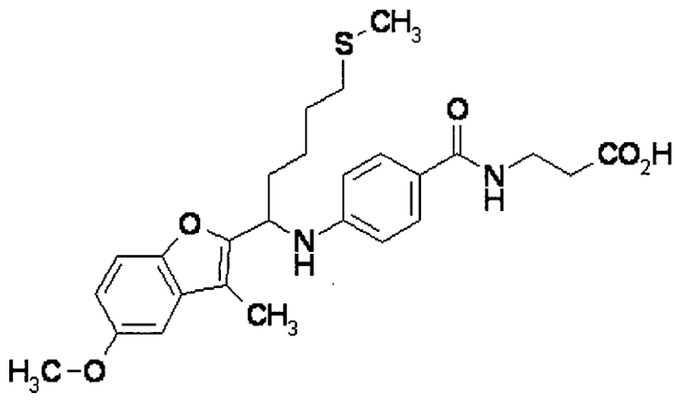
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objeto del título (153 mg, 56%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 (t, J = 6,6 Hz, 3 H), 1,16 - 1,44 (m, 8 H), 1,86 - 2,02 (m, 2 H), 2,24 (s, 3 H), 2,64 (t, J = 6,6 Hz, 2 H), 3,02 (s, 3 H), 3,69 (t, J = 6,6 Hz, 2 H), 3,84 (s, 3 H), 4,59 (t, J = 7,3 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,83 (dd, J = 8,8, 2,5 Hz, 1 H), 6,89 (d, J = 2,5 Hz, 1 H), 7,20 - 7,29 (m, 3 H).

Ejemplo A120

Ácido 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentil]amino}fenil)carbonil]amino}propanoico




(1)5-cloro-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentan-1-ona

A una mezcla de 5-metoxi-3-metil-1-benzofurano (2,00 g) sintetizado en el Ejemplo A104(2) anterior, cloruro de 5-clorovalerilo (1,74 mL) y nitrometano (40 mL) se añadió cloruro de aluminio (2,47 g) a 0 °C y la mezcla se agitó durante 2 h. Se añadió agua para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El

extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (5% de acetato de etilo/hexano) para dar el compuesto objeto del título (2,63 g, 76%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,83 - 1,97 (m, 4 H), 2,58 (s, 3 H), 2,98 - 3,05 (m, 2 H), 3,56 - 3,63 (m, 2 H), 3,87 (s, 3 H), 7,00 (d, J = 2,7 Hz, 1 H), 7,08 (dd, J = 9,0, 2,7 Hz, 1 H), 7,38 (d, J = 9,0 Hz, 1 H).

(2) 1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentan-1-ona

A una mezcla de 5-cloro-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentan-1-ona (1,30 g) sintetizada con anterioridad, metanol (15 mL) y tetrahidrofurano (15 mL) se añadió una solución acuosa al 15% (4,33 mL) de metanotiolato de sodio y la mezcla se agitó a temperatura ambiente durante 1 h y a 50 °C durante 1 h. Se agregó metanotiolato de sodio (325 mg) adicionalmente y la mezcla se agitó a 50 °C durante 1 h. Además, se añadió metanotiolato de sodio (325 mg) nuevamente y la mezcla se agitó a 50 °C durante 1 h. Se añadió agua para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con hexano para dar el compuesto objeto del título (492 mg, 36%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,64 - 1,79 (m, 2 H), 1,79 - 1,92 (m, 2 H), 2,11 (s, 3 H), 2,51 - 2,62 (m, 5 H), 3,00 (t,

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J = 7,3 Hz, 2 H), 3,87 (s, 3 H), 7,00 (d, J = 2,5 Hz, 1 H), 7,08 (dd, J = 9,1, 2,5 Hz, 1 H), 7,38 (d, J = 9,1 Hz, 1 H).

(3) 4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentil]amino}benzoato de metilo

A una mezcla de 1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentan-1-ona (658 mg) sintetizada con anterioridad, 4-aminobenzoato de metilo (375 mg), trietilamina (2,50 mL) y cloruro de metileno (10 mL) se añadió una solución 1,0 M (2,70 mL) de cloruro de titanio (IV) en cloruro de metileno a 0 °C y la mezcla se agitó bajo una atmósfera de argón a temperatura ambiente durante 3,5 días. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción, el cloruro de metileno se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (10 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (647 µL) y cianoborohidruro de sodio (283 mg) y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 50% de acetato de etilo/hexano) para dar el

compuesto objeto del título (645 mg, 67%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,30 - 1,71 (m, 4 H), 1,91 - 2,08 (m, 5 H), 2,25 (s, 3 H), 2,46 (t, J = 7,3 Hz, 2 H), 3,81 (s, 3 H), 3,83 (s, 3 H), 4,52 (d, J = 8,0 Hz, 1 H), 4,59 - 4,70 (m, 1 H), 6,57 (d, J = 8,8 Hz, 2 H), 6,83 (dd, J = 8,7, 2,5 Hz, 1 H), 6,87 (d, J = 2,5 Hz, 1 H), 7,25 (d, J = 8,7 Hz, 1 H), 7,80 (d, J = 8,8 Hz, 2 H).

(4) ácido 4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentil]amino}benzoico

A una mezcla de 4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentil]amino}benzoato de metilo (1,01 g) sintetizado con anterioridad, tetrahidrofurano (10 mL) y etanol (10 mL) se añadió solución acuosa 1 N de hidróxido de sodio (10,0 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (20 mL) y ácido clorhídrico 1 N (10,0 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (915 mg, 94%) en forma de un sólido marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,29 - 1,70 (m, 4 H), 1,93 - 2,09 (m, 5 H), 2,25 (s, 3 H), 2,46 (t, J = 7,3 Hz, 2 H), 3,83 (s, 3 H), 4,65 (t, J = 7,3 Hz, 1 H), 6,57 (d, J = 8,8 Hz, 2 H), 6,83 (dd, J = 8,8, 2,5 Hz, 1 H), 6,88 (d, J = 2,5 Hz, 1 H), 7,25 (d, J = 8,8 Hz, 1 H), 7,86 (d, J = 8,8 Hz, 2 H).

(5) 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentil]amino}fenil)carbonil]amino}propanoato de etilo

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A una mezcla de ácido 4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentil]amino}benzoico (450 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (252 mg), monohidrato de 1-hidroxibenzotriazol (251 mg), trietilamina (456 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (314 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (518 mg, 93%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,25 (t, J = 7,1 Hz, 3 H), 1,31 - 1,72 (m, 4 H), 1,91 - 2,10 (m, 5 H), 2,25 (s, 3 H), 2,42 - 2,50 (m, 2 H), 2,59 (t, J = 5,8 Hz, 2 H), 3,61 - 3,71 (m, 2 H), 3,84 (s, 3 H), 4,07 - 4,19 (m, 2 H), 4,38 - 4,45 (m, 1 H), 4,57 - 4,68 (m, 1 H), 6,54 - 6,66 (m, 3 H), 6,83 (dd, J = 8,7, 2,5 Hz, 1 H), 6,88 (d, J = 2,5 Hz, 1 H), 7,25 (d, J = 8,7 Hz, 1 H), 7,56 (d, J = 8,8 Hz, 2 H).

(6) ácido 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentil]amino}fenil)carbonil]amino}propanoico

A una mezcla de 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-

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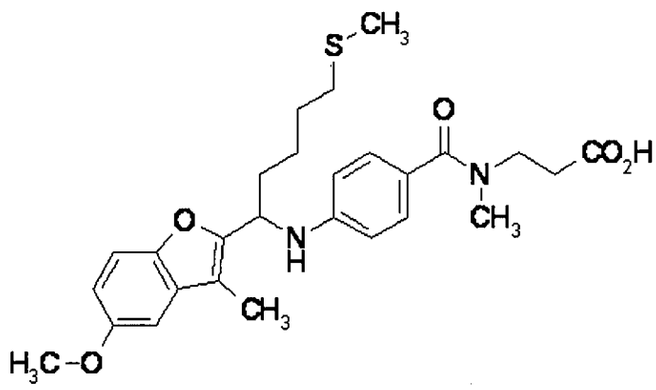
(metilsulfanil)pentil]amino}fenil)carbonil]amino}propanoato de etilo (253 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 3 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (133 mg, 56%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,30 - 1,69 (m, 4 H), 1,90 - 2,04 (m, 2 H), 2,05 (s, 3 H), 2,24 (s, 3 H), 2,41 - 2,50 (m, 2 H), 2,63 (t, J = 5,8 Hz, 2 H), 3,59 - 3,69 (m, 2 H), 3,83 (s, 3 H), 4,62 (t, J = 7,3 Hz, 1 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,65 (t, J = 5,9 Hz, 1 H), 6,83 (dd, J = 8,8, 2,5 Hz, 1 H), 6,88 (d, J = 2,5 Hz, 1 H), 7,22 - 7,28 (m, 1 H), 7,54 (d, J = 8,7 Hz, 2 H).

Ejemplo A121

Ácido 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentil]amino}fenil)carbonil](metil)amino}propanoico

1464



(1) 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentil]amino}benzoico (460 mg) sintetizado en el Ejemplo A120(4), 3-(metilamino)propanoato de etilo (219 mg), monohidrato de 1-hidroxibenzotriazol (256 mg), trietilamina (464 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (320 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 50% de acetato de

etilo/hexano) para dar el compuesto objeto del título (514 mg, 88%) en forma de un aceite de color marrón pálido.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,23 (t, J = 7,1 Hz, 3 H), 1,30 - 1,73 (m, 4 H), 1,88 - 2,10 (m, 5 H), 2,24 (s, 3 H), 2,41 - 2,50 (m, 2 H), 2,55 - 2,67 (m, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,3 Hz, 2 H), 3,84 (s, 3 H), 4,11 (q, J = 7,1 Hz, 2 H), 4,27 - 4,35 (m, 1 H), 4,54 - 4,65 (m, 1 H), 6,57 (d, J = 8,8 Hz, 2 H), 6,83 (dd, J = 8,8, 2,6 Hz, 1 H), 6,88 (d, J = 2,6 Hz, 1 H), 7,18 - 7,30 (m, 3 H).
(2) ácido 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentil]amino}fenil)carbonil](metil)amino}propanoico

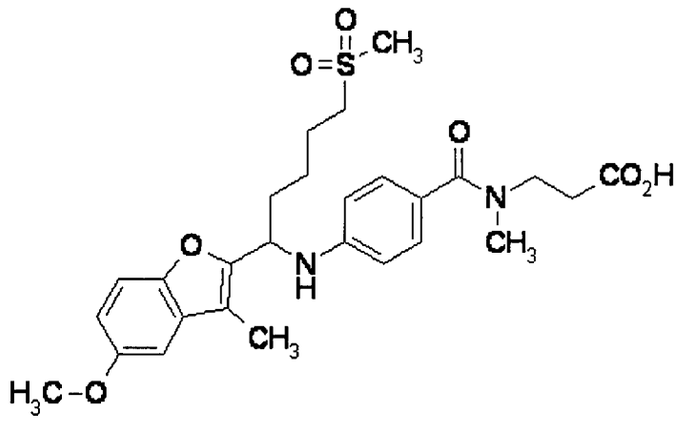
A una mezcla de 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentil]amino}fenil)carbonil](metil)amino}propanoato de etilo (251 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 3 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (74,8 mg, 33%) en forma de un sólido de color marrón pálido.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,30 - 1,69 (m, 4 H), 1,90 - 2,05 (m, 2 H), 2,06 (s, 3 H), 2,24 (s, 3 H), 2,46 (t, J = 6,8 Hz, 2 H), 2,66 (t, J = 6,6 Hz, 2 H), 3,03 (s, 3 H), 3,70 (t, J = 6,6 Hz, 2 H), 3,84 (s, 3 H), 4,60 (t, J = 7,3 Hz, 1 H),

1466

6,57 (d, J = 8,9 Hz, 2 H), 6,84 (dd, J = 8,9, 2,5 Hz, 1 H), 6,89 (d, J = 2,5 Hz, 1 H), 7,21 - 7,30 (m, 3 H).

Ejemplo A122

Ácido 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentil]amino}fenil)carbonil](metil)amino}propanoico



(1) 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfonil)pentil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una solución (10 mL) de 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfanil)pentil]amino}fenil)carbonil](metil)amino}propanoato de etilo (263 mg) sintetizado en el Ejemplo A121(1) en acetona se añadió ácido m-cloroperbenzoico (con contenido de agua, pureza del 69-75%) (344 mg) a 0 °C y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de sulfito de sodio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El

extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano), luego por cromatografía en columna de gel de sílice NH (acetato de etilo) para dar el compuesto objeto del título (104 mg, 37%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,24 (t, J = 7,1 Hz, 3 H), 1,34 - 1,69 (m, 2 H), 1,76 - 2,14 (m, 4 H), 2,24 (s, 3 H), 2,62 (t, J = 6,9 Hz, 2 H), 2,85 (s, 3 H), 2,97 (t, J = 8,0 Hz, 2 H), 3,02 (s, 3 H), 3,71 (t, J = 6,9 Hz, 2 H), 3,84 (s, 3 H), 4,12 (q, J = 7,1 Hz, 2 H), 4,30 (d, J = 8,0 Hz, 1 H), 4,57 - 4,68 (m, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 6,85 (dd, J = 8,7, 2,5 Hz, 1 H), 6,89 (d, J = 2,5 Hz, 1 H), 7,19 - 7,31 (m, 3 H).

(2) ácido 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfonil)pentil]amino}fenil)carbonil](metil)amino}propanoico

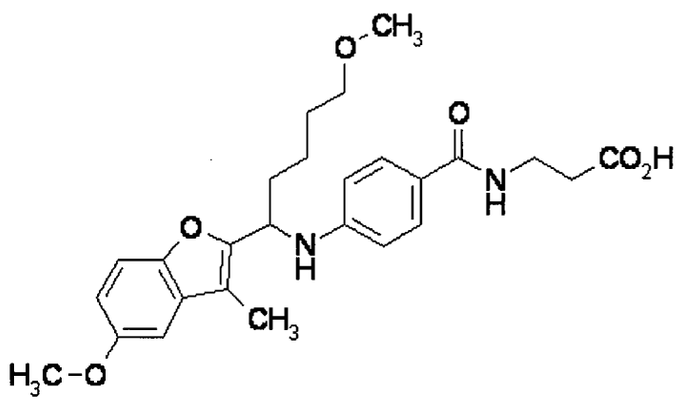
A una mezcla de 3-{[(4-{[1-(5-metoxi-3-metil-1-benzofuran-2-il)-5-(metilsulfonil)pentil]amino}fenil)carbonil](metil)amino}propanoato de etilo (104 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El

precipitado resultante se recogió por filtración para dar el compuesto objeto del título (52,7 mg, 53%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,34 - 1,69 (m, 2 H), 1,76 - 2,13 (m, 4 H), 2,23 (s, 3 H), 2,66 (t, J = 6,4 Hz, 2 H), 2,85 (s, 3 H), 2,96 (t, J = 7,8 Hz, 2 H), 3,04 (s, 3 H), 3,70 (t, J = 6,4 Hz, 2 H), 3,84 (s, 3 H), 4,59 - 4,66 (m, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 6,85 (dd, J = 9,1, 2,5 Hz, 1 H), 6,89 (d, J = 2,5 Hz, 1 H), 7,21 - 7,30 (m, 3 H).

Ejemplo A123

Ácido 3-{[(4-{[5-metoxi-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentil]amino}fenil)carbonil]amino}propanoico




(1) 5-metoxi-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentan-1-ona

A una solución (20 mL) de 5-cloro-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentan-1-ona (1,93 g) sintetizada en el Ejemplo A120(1) en metanol se añadieron yoduro de sodio (1,54 g) y metóxido de sodio (1,86 g) y la mezcla se agitó durante

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la noche con calentamiento a reflujo y se concentró a presión reducida. Se añadió agua al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 20% de acetato de etilo/hexano) para dar el compuesto objeto del título (797 mg, 42%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,62 - 1,75 (m, 2 H), 1,76 - 1,89 (m, 2 H), 2,58 (s, 3 H), 3,00 (t, J = 7,3 Hz, 2 H), 3,33 (s, 3 H), 3,43 (t, J = 6,3 Hz, 2 H), 3,87 (s, 3 H), 7,00 (d, J = 2,4 Hz, 1 H), 7,07 (dd, J = 9,0, 2,4 Hz, 1 H), 7,38 (d, J = 9,0 Hz, 1 H).

(2) 4-{[5-metoxi-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentil]amino}benzoato de metilo

A una mezcla de 5-metoxi-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentan-1-ona (797 mg) sintetizada con anterioridad, 4-aminobenzoato de metilo (479 mg), trietilamina (3,21 mL) y cloruro de metileno (10 mL) se añadió una solución 1,0 M (3,46 mL) de cloruro de titanio (IV) en cloruro de metileno a 0 °C y la mezcla se agitó bajo una atmósfera de argón a temperatura ambiente durante 3,5 días. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (10 mL) del aceite obtenido en

tetrahidrofurano se añadieron ácido acético (824 µL) y cianoborohidruro de sodio (362 mg) y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 40% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,07 g, 90%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,27 - 1,67 (m, 4 H), 1,91 - 2,08 (m, 2 H), 2,24 (s, 3 H), 3,30 (s, 3 H), 3,31 - 3,37 (m, 2 H), 3,81 (s, 3 H), 3,83 (s, 3 H), 4,51 - 4,56 (m, 1 H), 4,60 - 4,69 (m, 1 H), 6,56 (d, J = 8,8 Hz, 2 H), 6,83 (dd, J = 8,8, 2,5 Hz, 1 H), 6,87 (d, J = 2,5 Hz, 1 H), 7,25 (d, J = 8,8 Hz, 1 H), 7,80 (d, J = 8,8 Hz, 2 H).

(3) ácido 4-{[5-metoxi-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentil]amino}benzoico

A una mezcla de 4-{[5-metoxi-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentil]amino}benzoato de metilo (1,07 g) sintetizado con anterioridad, tetrahidrofurano (10 mL) y etanol (10 mL) se añadió solución acuosa 1 N de hidróxido de sodio (10,0 mL) y la mezcla se agitó con calentamiento a reflujo durante 1 día y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (10,0 mL) se añadió a 0 °C. El precipitado resultante se

recogió por filtración para dar el compuesto objeto del título (875 mg, 85%) en forma de un sólido marrón.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,26 - 1,68 (m, 4 H), 1,90 - 2,10 (m, 2 H), 2,25 (s, 3 H), 3,30 (s, 3 H), 3,35 (t, J = 6,5 Hz, 2 H), 3,84 (s, 3 H), 4,66 (t, J = 7,3 Hz, 1 H), 6,58 (d, J = 8,8 Hz, 2 H), 6,84 (dd, J = 8,9, 2,5 Hz, 1 H), 6,89 (d, J = 2,5 Hz, 1 H), 7,26 (d, J = 8,9 Hz, 1 H), 7,86 (d, J = 8,8 Hz, 2 H).

(4) 3-{[(4-{[5-metoxi-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[5-metoxi-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentil]amino}benzoico (400 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (234 mg), monohidrato de 1-hidroxibenzotriazol (233 mg), trietilamina (422 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (291 mg) y la mezcla se agitó a temperatura ambiente durante 2,5 días. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (40 - 80% de acetato de etilo/hexano) para dar el compuesto objeto del título (489 mg, 97%) en forma de un aceite de color marrón pálido

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,25 (t, J = 7,1 Hz, 3 H), 1,30 - 1,69 (m, 4 H), 1,88 - 2,08 (m, 2 H), 2,24 (s, 3 H), 2,55 - 2,62 (m, 2 H), 3,30 (s, 3 H), 3,34 (t, J = 6,7 Hz, 2 H), 3,62 - 3,70 (m, 2 H), 3,83 (s, 3 H), 4,14 (q, J = 7,1 Hz, 2 H), 4,39 - 4,47 (m, 1 H), 4,57 - 4,68 (m, 1 H), 6,54 - 6,64 (m, 3 H), 6,82 (dd, J = 8,8, 2,4 Hz, 1 H), 6,87 (d, J = 2,4 Hz, 1 H), 7,24 (d, J = 8,8 Hz, 1 H), 7,55 (d, J = 8,8 Hz, 2 H).

(5) ácido 3-{[(4-{[5-metoxi-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentil]amino}fenil)carbonil]amino}propanoico

A una mezcla de 3-{[(4-{[5-metoxi-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentil]amino}fenil)carbonil]amino}propanoato de etilo (489 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 3 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración y el sólido obtenido se disolvió en acetato de etilo. La solución se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (453 mg, 98%) en forma de un sólido de color marrón pálido.

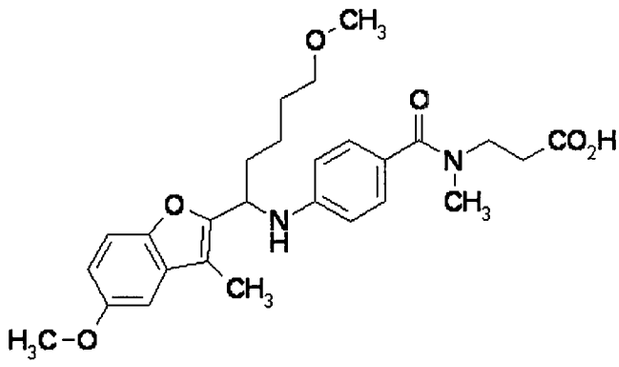
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,27 - 1,67 (m, 4 H), 1,91 - 2,03 (m, 2 H), 2,23 (s, 3 H), 2,63 (t, J = 5,7 Hz, 2 H), 3,30 (s, 3 H), 3,35 (td, J = 6,3, 1,2 Hz, 2 H), 3,60 - 3,69 (m, 2 H), 3,83 (s, 3 H), 4,61 (t, J = 7,2 Hz, 1 H), 6,56 (d, J = 8,8 Hz, 2 H), 6,66 (t, J = 6,0 Hz, 1 H), 6,82 (dd, J = 8,9,

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2,5 Hz, 1 H), 6,87 (d, J = 2,5 Hz, 1 H), 7,22 - 7,27 (m, 1 H), 7,54 (d, J = 8,8 Hz, 2 H).

Ejemplo A124

Ácido 3-{[(4-{[5-metoxi-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentil]amino}fenil)carbonil](metil)amino}propanoico



(1) 3-{[(4-{[5-metoxi-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[5-metoxi-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentil]amino}benzoico (400 mg) sintetizado en el Ejemplo A123(3), 3-(metilamino)propanoato de etilo (199 mg), monohidrato de 1-hidroxibenzotriazol (233 mg), trietilamina (422 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (291 mg) y la mezcla se agitó a temperatura ambiente durante 2,5 días. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de

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carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (40 - 80% de acetato de etilo/hexano) para dar el compuesto objeto del título (460 mg, 89%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,24 (t, J = 7,1 Hz, 3 H), 1,30 - 1,67 (m, 4 H), 1,88 - 2,06 (m, 2 H), 2,24 (s, 3 H), 2,62 (t, J = 7,0 Hz, 2 H), 3,02 (s, 3 H), 3,30 (s, 3 H), 3,35 (t, J = 6,3 Hz, 2 H), 3,71 (t, J = 7,0 Hz, 2 H), 3,84 (s, 3 H), 4,12 (q, J = 7,1 Hz, 2 H), 4,27 - 4,36 (m, 1 H), 4,55 - 4,66 (m, 1 H), 6,57 (d, J = 8,8 Hz, 2 H), 6,83 (dd, J = 8,8, 2,5 Hz, 1 H), 6,88 (d, J = 2,5 Hz, 1 H), 7,18 - 7,28 (m, 3 H).

(2) ácido 3-{[(4-{[5-metoxi-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentil]amino}fenil)carbonil](metil)amino}propanoico

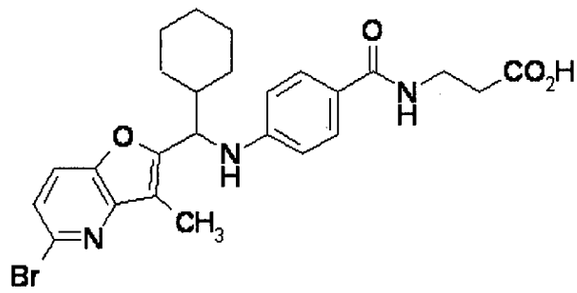
A una mezcla de 3-{[(4-{[5-metoxi-1-(5-metoxi-3-metil-1-benzofuran-2-il)pentil]amino}fenil)carbonil](metil)amino}propanoato de etilo (460 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó durante la noche a temperatura ambiente y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (428 mg, 99%) en forma de un sólido amarillo pálido.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,27 - 1,67 (m, 4 H), 1,88 - 2,06 (m, 2 H), 2,23 (s, 3 H), 2,67 (t, J = 6,6 Hz, 2 H), 3,04 (s, 3 H), 3,30 (s, 3 H), 3,35 (td, J = 6,4, 1,0 Hz, 2 H), 3,70 (t, J = 6,6 Hz, 2 H), 3,84 (s, 3 H), 4,61 (t, J = 7,2 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,83 (dd, J = 8,8, 2,4 Hz, 1 H), 6,88 (d, J = 2,4 Hz, 1 H), 7,21 - 7,30 (m, 3 H).

Ejemplo A125

Ácido 3-{[(4-{[(5-bromo-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico




(1) 3-(benciloxi)-6-bromopiridin-2-carbonitrilo

A una mezcla de 2-ciano-3-hidroxipiridina (10,0 g), agua (40 mL) y acetonitrilo (200 mL) se añadió N-bromosuccinimida (17,8 g) a 0 °C y la mezcla se agitó a 0 °C durante 2 h y a temperatura ambiente durante 1 h. Se añadió acetato de etilo a la mezcla de reacción. La solución se lavó con agua y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido blanco. A una solución (200 mL) del sólido obtenido en acetona se añadieron bromuro de bencilo (11,9 mL) y carbonato de potasio (23,1 g) y la mezcla se agitó durante la noche con calentamiento a

reflujo. El material insoluble se filtró y el filtrado se concentró a presión reducida. El residuo se lavó con metanol y tolueno para dar el compuesto objeto del título (3,17 g, 13%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, DMSO-d) δ ppm 5,36 (s, 2 H), 7,32 - 7,50 (m, 5 H), 7,87 (d, J = 9,1 Hz, 1 H), 7,96 (d, J = 9,1 Hz, 1 H).

(2) 1-[3-(benciloxi)-6-bromopiridin-2-il]etanona

A una solución (40 mL) de 3-(benciloxi)-6-bromopiridin-2-carbonitrilo (4,00 g) sintetizado con anterioridad en tetrahidrofurano se añadió una solución 1,0 M (27,6 mL) de bromuro de metilmagnesio en tetrahidrofurano a 0 °C y la mezcla se agitó a temperatura ambiente durante 5 h. Se añadió además una solución 1,0 M (13,8 mL) de bromuro de metilmagnesio en tetrahidrofurano y la mezcla luego se agitó a temperatura ambiente durante 1 h, luego se añadió ácido clorhídrico 1 N (80 mL). La mezcla se agitó durante la noche a temperatura ambiente, una solución acuosa 1 N de hidróxido de sodio (100 mL) se añadió y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (10 - 90% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,45 g, 34%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,65 (s, 3 H), 5,18 (s, 2 H), 7,25 (d, J = 8,5 Hz, 1 H), 7,28 - 7,46 (m, 5 H), 7,48 (d, J = 8,5 Hz, 1 H).

(3) 1-(6-bromo-3-hidroxipiridin-2-il)etanona

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A una suspensión (30 mL) de cloruro de aluminio (3,96 g) en tolueno se añadió cloruro de trimetilamonio (1,32 g) y la mezcla se agitó bajo una atmósfera de argón a temperatura ambiente durante 1 h. Una solución (30 mL) de 1-[3-(benciloxi)-6-bromopiridin-2-il]etanona (2,81 g) sintetizada con anterioridad en tolueno se añadió a la mezcla y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró a presión reducida, una solución saturada acuosa de sal de Rochelle se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 5% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,64 g, 83%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,74 (s, 3 H), 7,23 (d, J = 8,8 Hz, 1 H), 7,52 (d, J = 8,8 Hz, 1 H), 11,77 (s, 1 H).

(4) (5-bromo-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metanona

A una mezcla de 1-(6-bromo-3-hidroxipiridin-2-il)etanona (1,64 g) sintetizada con anterioridad, 2-bromo-1-ciclohexiletanona (2,34 g) sintetizado en el Ejemplo A51(1) y N,N-dimetilformamida (20 mL) se añadió carbonato de potasio (3,15 g) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a

presión reducida. El residuo se lavó con éter diisopropílico para dar el compuesto objeto del título (865 mg, 35%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,19 - 1,54 (m, 5 H), 1,70 - 1,81 (m, 1 H), 1,81 - 2,00 (m, 4 H), 2,63 (s, 3 H), 3,23 - 3,35 (m, 1 H), 7,52 (d, J = 8,7 Hz, 1 H), 7,69 (d, J = 8,7 Hz, 1 H).

(5) 4-{[(5-bromo-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}benzoato de metilo

A una mezcla de (5-bromo-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metanona (1,46 g) sintetizada con anterioridad, 4-aminobenzoato de metilo (753 mg), trietilamina (5,05 mL) y cloruro de metileno (15 mL) se añadió una solución 1,0 M (5,44 mL) de cloruro de titanio (IV) en cloruro de metileno a 0 °C y la mezcla se agitó bajo una atmósfera de argón durante la noche a temperatura ambiente. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (20 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (1,30 mL) y cianoborohidruro de sodio (569 mg) y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó

sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 40% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,86 g, 90%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 1,35 (m, 5 H), 1,45 - 1,55 (m, 1 H), 1,63 - 2,00 (m, 4 H), 2,04 - 2,14 (m, 1 H), 2,33 (s, 3 H), 3,82 (s, 3 H), 4,43 - 4,54 (m, 2 H), 6,55 (d, J = 9,0 Hz, 2 H), 7,29 (d, J = 8,5 Hz, 1 H), 7,48 (d, J = 8,5 Hz, 1 H), 7,80 (d, J = 9,0 Hz, 2 H).

(6) ácido 4-{[(5-bromo-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}benzoico

A una solución (20 mL) de 4-{[(5-bromo-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}benzoato de metilo (1,86 g) sintetizado con anterioridad en tetrahidrofurano se añadió solución acuosa 2 N de hidróxido de litio (10,2 mL) y la mezcla se agitó con calentamiento a reflujo durante 2 h. Se añadió además una solución acuosa 4 N de hidróxido de litio (5,10 mL) y la mezcla se agitó con calentamiento a reflujo durante 4 h. Una solución acuosa 4 N de hidróxido de litio (5,10 mL) y etanol (20 mL) se añadieron luego y la mezcla se agitó con calentamiento a reflujo durante 4 h y se concentró a presión reducida. El residuo se disolvió en agua (40 mL) y ácido clorhídrico 1 N (61,2 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (1,74 g, 96%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,41 (m, 6 H), 1,54 - 1,81 (m, 3 H), 1,87 - 2,02 (m, 1 H), 2,02 - 2,15 (m, 1 H), 2,27 (s, 3 H), 4,52 - 4,62 (m, 1 H), 6,63 (d, J = 8,7 Hz, 2 H), 6,92 (d, J = 8,0 Hz, 1 H), 7,43 (d, J = 8,7 Hz, 1 H), 7,61 (d, J = 8,7 Hz, 2 H), 7,90 (d, J = 8,7 Hz, 1 H), 12,01 (br s, 1 H).

(7) 3-{[(4-{[(5-bromo-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[(5-bromo-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}benzoico (300 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (157 mg), monohidrato de 1-hidroxibenzotriazol (156 mg), trietilamina (283 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (196 mg) y la mezcla se agitó a temperatura ambiente durante 1,5 días. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (20 - 60% de acetato de etilo/hexano) para dar el compuesto objeto del título (343 mg, 93%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,37 (m, 8 H), 1,44 - 1,55 (m, 1 H), 1,61 - 1,98 (m, 4 H), 2,02 - 2,13 (m, 1 H),

2,31 (s, 3 H), 2,58 (t, J = 5,9 Hz, 2 H), 3,61 - 3,70 (m, 2 H), 4,13 (q, J = 7,1 Hz, 2 H), 4,40 - 4,50 (m, 2 H), 6,55 (d, J = 8,8 Hz, 2 H), 6,63 (t, J = 5,9 Hz, 1 H), 7,27 (d, J = 8,5 Hz, 1 H), 7,47 (d, J = 8,5 Hz, 1 H), 7,54 (d, J = 8,8 Hz, 2 H).

(8) ácido 3-{[(4-{[(5-bromo-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico

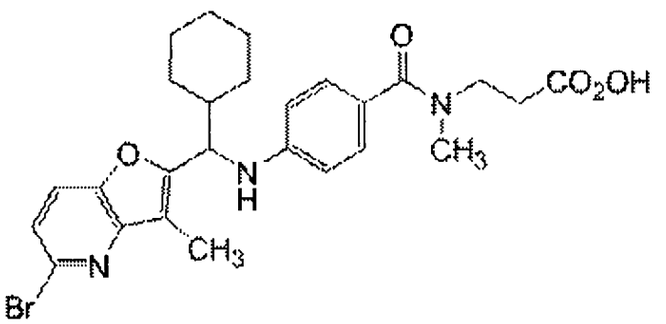
A una mezcla de 3-{[(4-{[(5-bromo-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoato de etilo (343 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de litio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (307 mg, 94%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, DMSO-d6) δ ppm 0,94 - 1,30 (m, 5 H), 1,30 - 1,42 (m, 1 H), 1,53 - 1,82 (m, 3 H), 1,86 - 2,02 (m, 1 H), 2,03 - 2,15 (m, 1 H), 2,26 (s, 3 H), 2,41 (t, J = 7,1 Hz, 2 H), 3,29 - 3,41 (m, 2 H), 4,56 (t, J = 8,2 Hz, 1 H), 6,60 (d, J = 8,9 Hz, 2 H), 6,66 (d, J = 8,2 Hz, 1 H), 7,42 (d, J = 8,6 Hz, 1 H), 7,52 (d, J = 8,9 Hz, 2 H), 7,89 (d, J = 8,6 Hz, 1 H), 8,01 (t, J = 5,5 Hz, 1 H).

Ejemplo A126

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Ácido 3-{[(4-{[(5-bromo-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) 3-{[(4-{[(5-bromo-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[(5-bromo-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}benzoico (300 mg) sintetizado en el Ejemplo A125(6), 3-(metilamino)propanoato de etilo (134 mg), monohidrato de 1-hidroxibenzotriazol (156 mg), trietilamina (283 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (196 mg) y la mezcla se agitó a temperatura ambiente durante 1,5 días. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de

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sílice (20 - 60% de acetato de etilo/hexano) para dar el compuesto objeto del título (317 mg, 84%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,38 (m, 8 H), 1,44 - 1,55 (m, 1 H), 1,59 - 2,00 (m, 4 H), 2,02 - 2,14 (m, 1 H), 2,32 (s, 3 H), 2,56 - 2,66 (m, 2 H), 3,00 (s, 3 H), 3,69 (t, J = 7,0 Hz, 2 H), 4,06 - 4,17 (m, 2 H), 4,27 - 4,34 (m, 1 H), 4,39 - 4,46 (m, 1 H), 6,53 (d, J = 8,7 Hz, 2 H), 7,20 (d, J = 8,7 Hz, 2 H), 7,28 (d, J = 8,5 Hz, 1 H), 7,48 (d, J = 8,5 Hz, 1 H).

(2) ácido 3-{[(4-{[(5-bromo-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico

A una mezcla de 3-{[(4-{[(5-bromo-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (271 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de litio (1,00 mL) y la mezcla se agitó durante la noche a temperatura ambiente y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (271 mg, 90%) en forma de un sólido amarillo pálido.

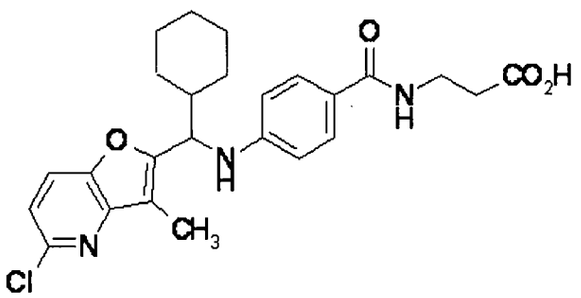
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,37 (m, 5 H), 1,44 - 1,55 (m, 1 H), 1,60 - 1,97 (m, 4 H), 2,03 - 2,14 (m, 1 H), 2,31 (s, 3 H), 2,64 (t, J = 6,3 Hz, 2 H), 3,02 (s, 3 H), 3,69

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(t, J = 6,3 Hz, 2 H), 4,43 (d, J = 7,9 Hz, 1 H), 6,54 (d, J = 8,6 Hz, 2 H), 7,23 (d, J = 8,6 Hz, 2 H), 7,29 (d, J = 8,6 Hz, 1 H), 7,49 (d, J = 8,6 Hz, 1 H).

Ejemplo A127

Ácido 3-{[(4-{[(5-cloro-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico



(1) 3-(benciloxi)-6-cloro-2-yodopiridina

A una solución acuosa (100 mL) de 2-cloro-5-hidroxipiridina (10,0 g) se añadieron carbonato de sodio (16,3 g) y yodo (10,8 g) y la mezcla se agitó a temperatura ambiente durante 5 días. La mezcla de reacción se acidificó hasta pH = 5 con ácido clorhídrico 1 N y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido amarillo. El sólido obtenido se recristalizó en metanol para dar un sólido marrón. A una solución (200 mL) del sólido obtenido en acetona se añadieron bromuro de bencilo (8,02 mL) y carbonato de potasio (15,5 g) y la mezcla se agitó durante la noche con calentamiento a reflujo. Insoluble material se filtró y el filtrado se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 -

30% de acetato de etilo/hexano) para dar el compuesto objeto del título (18,4 g, 69%) en forma de un aceite amarillo. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 5,17 (s, 2 H), 6,97 (d, J = 8,4 Hz, 1 H), 7,15 (d, J = 8,4 Hz, 1 H), 7,30 - 7,47 (m, 5 H).

(2) 1-[3-(benciloxi)-6-cloropiridin-2-il]etanol

A una solución (100 mL) de 3-(benciloxi)-6-cloro-2-yodopiridina (17,4 g) sintetizada con anterioridad en tetrahidrofurano se añadió una solución 1,0 M (60,2 mL) de bromuro de isopropilmagnesio en tetrahidrofurano a -45 °C y la mezcla se agitó a la misma temperatura durante 1 h. Acetaldehído (10,2 mL) se añadió a la mezcla de reacción y la mezcla se agitó a -45 °C durante 30 min, luego a temperatura ambiente durante 2 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción, el tetrahidrofurano se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 30% de acetato de etilo/hexano) para dar el compuesto objeto del título (6,82 g, 52%) en forma de un aceite amarillo pálido. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,46 (d, J = 6,6 Hz, 3 H), 3,95 (d, J = 7,7 Hz, 1 H), 5,06 - 5,18 (m, 3 H), 7,14 (d, J = 8,5 Hz, 1 H), 7,17 (d, J = 8,5 Hz, 1 H), 7,31 - 7,44 (m, 5 H).

(3) 1-[3-(benciloxi)-6-cloropiridin-2-il]etanona

A una mezcla de 1-[3-(benciloxi)-6-cloropiridin-2-il]etanol (7,04 g) sintetizado con anterioridad, N-óxido de 4-metilmorfolina (6,26 g) y acetonitrilo (140 mL) se añadió

perrutenato de tetrapropilamonio (938 mg) y la mezcla se agitó a temperatura ambiente durante 3 h y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 10% de acetato de etilo/hexano) para dar el compuesto objeto del título (6,26 g, 90%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,66 (s, 3 H), 5,19 (s, 2 H), 7,27 - 7,47 (m, 7 H).

(4) 1-(6-cloro-3-hidroxipiridin-2-il)etanona

A una suspensión (80 mL) de cloruro de aluminio (14,3 g) en tolueno se añadió cloruro de trimetilamonio (4,75 g) y la mezcla se agitó bajo una atmósfera de argón a temperatura ambiente durante 1 h. A la mezcla se añadió una solución (80 mL) de 1-[3-(benciloxi)-6-cloropiridin-2-il]etanona (8,66 g) sintetizado con anterioridad en tolueno y la mezcla se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se concentró a presión reducida, una solución saturada acuosa de sal de Rochelle se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 5% de acetato de etilo/hexano) para dar el compuesto objeto del título (4,89 g, 86%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,74 (s, 3 H), 7,31 (d, J = 8,8 Hz, 1 H), 7,39 (d, J = 8,8 Hz, 1 H), 11,77 (s, 1 H).

(5) (5-cloro-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metanona

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A una mezcla de 1-(6-cloro-3-hidroxipiridin-2-il)etanona (4,89 g) sintetizada con anterioridad, 2-bromo-1-ciclohexiletanona (7,01 g) sintetizado en el Ejemplo A51(1) y N,N-dimetilformamida (50 mL) se añadió carbonato de potasio (11,8 g) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con éter diisopropílico para dar el compuesto objeto del título (5,78 g, 73%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,19 - 1,61 (m, 5 H), 1,70 - 1,80 (m, 1 H), 1,81 - 2,01 (m, 4 H), 2,63 (s, 3 H), 3,23 - 3,35 (m, 1 H), 7,39 (d, J = 8,7 Hz, 1 H), 7,78 (d, J = 8,7 Hz, 1 H).

(6) 4-{[(5-cloro-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}benzoato de metilo

A una mezcla de (5-cloro-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metanona (1,00 g) sintetizada con anterioridad, 4-aminobenzoato de metilo (599 mg), trietilamina (4,01 mL) y cloruro de metileno (10 mL) se añadió una solución 1,0 M (4,32 mL) de cloruro de titanio (IV) en cloruro de metileno a 0 °C y la mezcla se agitó bajo una atmósfera de argón durante la noche a temperatura ambiente. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se

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lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (15 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (1,03 mL) y cianoborohidruro de sodio (452 mg) y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 40% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,31 g, 81%) en forma de un sólido anaranjado.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 1,37 (m, 5 H), 1,45 - 1,56 (m, 1 H), 1,63 - 1,99 (m, 4 H), 2,03 - 2,14 (m, 1 H), 2,32 (s, 3 H), 3,81 (s, 3 H), 4,43 - 4,56 (m, 2 H), 6,54 (d, J = 9,0 Hz, 2 H), 7,14 (d, J = 8,5 Hz, 1 H), 7,56 (d, J = 8,5 Hz, 1 H), 7,79 (d, J = 9,0 Hz, 2 H).

(7) ácido 4-{[(5-cloro-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}benzoico

A una mezcla de 4-{[(5-cloro-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}benzoato de metilo (1,31 g) sintetizado con anterioridad, etanol (20 mL) y tetrahidrofurano (20 mL) se añadió solución acuosa 1 N de hidróxido de litio (20 mL) y la mezcla se agitó con calentamiento a reflujo durante 3 h y se concentró a presión reducida. El residuo se disolvió en agua (40 mL) y ácido

clorhídrico 1 N (20 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración y el sólido obtenido se disolvió en acetato de etilo. La solución se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con éter diisopropílico para dar el compuesto objeto del título (1,21 g, 96%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, DMSO-d6) δ ppm 0,96 - 1,42 (m, 6 H), 1,54 - 1,82 (m, 3 H), 1,87 - 2,03 (m, 1 H), 2,04 - 2,16 (m, 1 H), 2,28 (s, 3 H), 4,53 - 4,64 (m, 1 H), 6,64 (d, J = 8,9 Hz, 2 H), 6,95 (d, J = 7,9 Hz, 1 H), 7,32 (d, J = 8,6 Hz, 1 H), 7,62 (d, J = 8,9 Hz, 2 H), 7,99 (d, J = 8,6 Hz, 1 H), 12,02 (br s, 1 H).

(8) 3-{[(4-{[(5-cloro-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[(5-cloro-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}benzoico (300 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (174 mg), monohidrato de 1-hidroxibenzotriazol (173 mg), trietilamina (315 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (217 mg) y la mezcla se agitó a temperatura ambiente durante 2,5 días. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre

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sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (383 mg, cuantitativo) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 1,37 (m, 8 H), 1,45 - 1,56 (m, 1 H), 1,61 - 1,99 (m, 4 H), 2,02 - 2,14 (m, 1 H), 2,31 (s, 3 H), 2,54 - 2,62 (m, 2 H), 3,60 - 3,69 (m, 2 H), 4,13 (q, J = 7,1 Hz, 2 H), 4,40 - 4,50 (m, 2 H), 6,55 (d, J = 8,8 Hz, 2 H), 6,62 (t, J = 5,9 Hz, 1 H), 7,14 (d, J = 8,5 Hz, 1 H), 7,54 (d, J = 8,8 Hz, 2 H), 7,55 (d, J = 8,5 Hz, 1 H).

(9) ácido 3-{[(4-{[(5-cloro-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico

A una mezcla de 3-{[(4-{[(5-cloro-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil]amino}propanoato de etilo (383 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (328 mg, 93%) en forma de un sólido blanco.

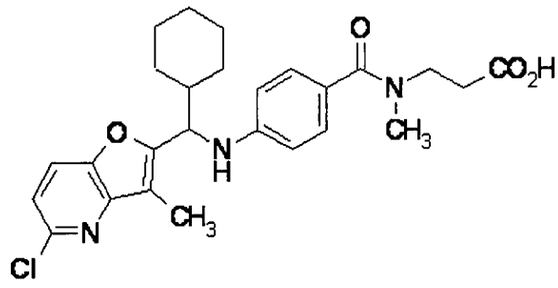
$^1$H RMN (300 MHz, DMSO-d6) δ ppm 0,95 - 1,30 (m, 5 H), 1,30 - 1,41 (m, 1 H), 1,55 - 1,82 (m, 3 H), 1,87 - 2,01 (m, 1 H), 2,04 - 2,16 (m, 1 H), 2,26 (s, 3 H), 2,42 (t, J = 7,2 Hz, 2 H), 3,26 - 3,42 (m, 2 H), 4,56 (t, J = 8,2 Hz, 1 H), 6,60 (d,

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J = 8,9 Hz, 2 H), 6,68 (d, J = 8,2 Hz, 1 H), 7,31 (d, J = 8,5 Hz, 1 H), 7,52 (d, J = 8,9 Hz, 2 H), 7,93 - 8,06 (m, 2 H).

Ejemplo A128

Ácido 3-{[(4-{[(5-cloro-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico



(1) 3-{[(4-{[(5-cloro-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[(5-cloro-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}benzoico (300 mg) sintetizado en el Ejemplo A127(7), 3-(metilamino)propanoato de etilo (148 mg), monohidrato de 1-hidroxibenzotriazol (173 mg), trietilamina (315 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (217 mg) y la mezcla se agitó a temperatura ambiente durante 2,5 días. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de

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carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (332 mg, 86%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 1,38 (m, 8 H), 1,44 - 1,56 (m, 1 H), 1,61 - 1,99 (m, 4 H), 2,03 - 2,15 (m, 1 H), 2,31 (s, 3 H), 2,61 (t, J = 6,9 Hz, 2 H), 3,00 (s, 3 H), 3,69 (t, J = 6,9 Hz, 2 H), 4,06 - 4,17 (m, 2 H), 4,29 - 4,36 (m, 1 H), 4,39 - 4,47 (m, 1 H), 6,54 (d, J = 8,7 Hz, 2 H), 7,14 (d, J = 8,5 Hz, 1 H), 7,21 (d, J = 8,7 Hz, 2 H), 7,56 (d, J = 8,5 Hz, 1 H).

(2) ácido 3-{[(4-{[(5-cloro-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico

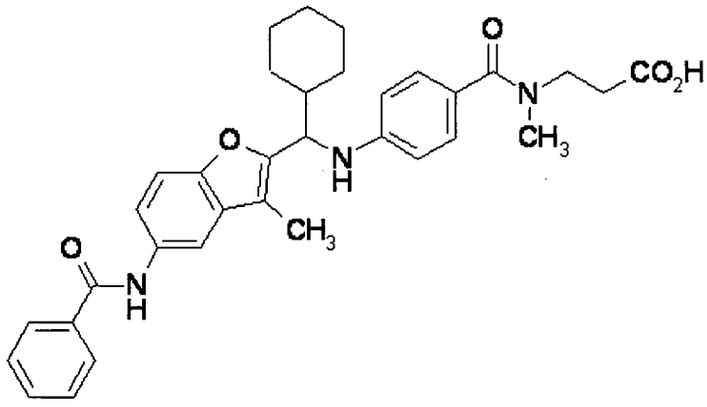
A una mezcla de 3-{[(4-{[(5-cloro-3-metilfuro[3,2-b]piridin-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (332 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de litio (3,00 mL) y la mezcla se agitó durante la noche a temperatura ambiente y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (3,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (278 mg, 89%) en forma de un sólido amarillo pálido.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,38 (m, 5 H), 1,44 - 1,56 (m, 1 H), 1,61 - 1,98 (m, 4 H), 2,02 - 2,15 (m, 1 H), 2,31 (s, 3 H), 2,62 (t, J = 6,3 Hz, 2 H), 3,00 (s, 3 H), 3,68 (t, J = 6,3 Hz, 2 H), 4,43 (d, J = 8,0 Hz, 1 H), 6,54 (d, J = 8,5 Hz, 2 H), 7,14 (d, J = 8,5 Hz, 1 H), 7,22 (d, J = 8,5 Hz, 2 H), 7,57 (d, J = 8,5 Hz, 1 H).

Ejemplo A129

Ácido 3-[({4-[(ciclohexil{3-metil-5-[(fenilcarbonil)amino]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico




A una solución (10 mL) de 3-{[(4-{[(5-amino-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (280 mg) sintetizado en el Ejemplo A110(5) en N,N-dimetilacetamida se añadió cloruro de benzoilo (99 µL) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo

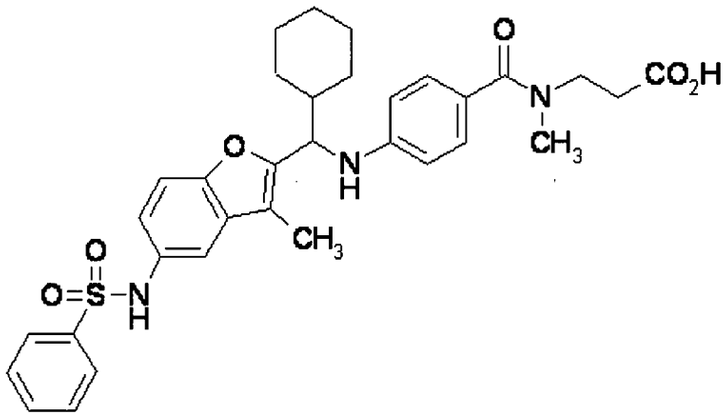
con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar un aceite de color rojo pálido. A una mezcla del aceite obtenido, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de litio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (303 mg, 94%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,38 (m, 5 H), 1,46 - 1,58 (m, 1 H), 1,60 - 1,99 (m, 4 H), 2,03 - 2,16 (m, 1 H), 2,19 (s, 3 H), 2,44 - 2,60 (m, 2 H), 2,96 (s, 3 H), 3,49 - 3,64 (m, 2 H), 4,36 (d, J = 8,0 Hz, 1 H), 6,54 (d, J = 8,7 Hz, 2 H), 7,13 - 7,33 (m, 4 H), 7,39 - 7,56 (m, 3 H), 7,80 (s, 1 H), 7,85 - 7,92 (m, 2 H), 8,21 (s, 1 H).

Ejemplo A130

Ácido 3-[({4-[(ciclohexil{3-metil-5-[(fenilsulfonil)amino]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

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(1) 3-[({4-[(ciclohexil{3-metil-5-[(fenilsulfonil)amino]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo

A una solución (10 mL) de 3-{[(4-{[(5-amino-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (254 mg) sintetizado en el Ejemplo A110(5) en N,N-dimetilacetamida se añadió cloruro de bencensulfonilo (99 µL) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (312 mg, 96%) en forma de un aceite incoloro.

1496

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 1,34 (m, 8 H), 1,41 - 1,54 (m, 1 H), 1,58 - 1,95 (m, 4 H), 2,04 - 2,12 (m, 1 H), 2,18 (s, 3 H), 2,56 - 2,68 (m, 2 H), 3,02 (s, 3 H), 3,71 (t, J = 6,7 Hz, 2 H), 4,12 (q, J = 7,1 Hz, 2 H), 4,28 - 4,39 (m, 2 H), 6,51 - 6,58 (m, 3 H), 6,78 (dd, J = 8,8, 2,2 Hz, 1 H), 7,14 - 7,24 (m, 4 H), 7,37 - 7,46 (m, 2 H), 7,48 - 7,56 (m, 1 H), 7,68 - 7,74 (m, 2 H).

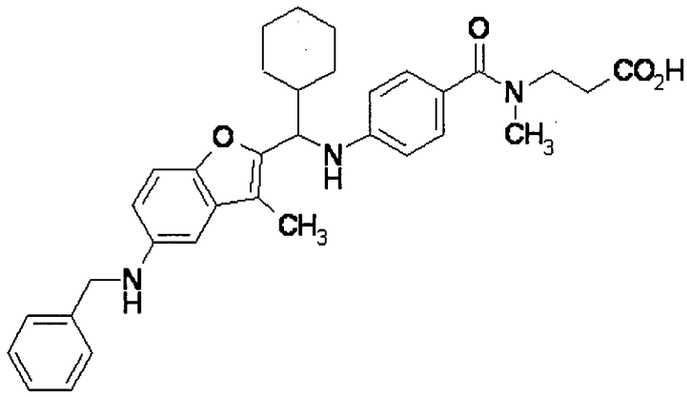
(2) ácido 3-[({4-[(ciclohexil{3-metil-5-[(fenilsulfonil)amino]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

A una mezcla de 3-[({4-[(ciclohexil{3-metil-5-[(fenilsulfonil)amino]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo (312 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (240 mg, 80%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,89 - 1,37 (m, 5 H), 1,40 - 1,55 (m, 1 H), 1,58 - 1,97 (m, 4 H), 2,02 - 2,13 (m, 1 H), 2,16 (s, 3 H), 2,62 (t, J = 6,1 Hz, 2 H), 3,01 (s, 3 H), 3,68 (t, J = 6,1 Hz, 2 H), 4,34 (d, J = 8,0 Hz, 1 H), 6,53 (d, J = 8,7 Hz, 2 H), 6,79 (dd, J = 8,7, 2,3 Hz, 1 H), 6,84 - 6,98 (m, 1 H), 7,11 - 7,25 (m, 4 H), 7,34 - 7,42 (m, 2 H), 7,45 - 7,53 (m, 1 H), 7,67 - 7,74 (m, 2 H).

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Ejemplo A131

Ácido 3-[{[4-({[5-(bencilamino)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoico



(1) 3-[{[4-({[5-(bencilamino)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

A una mezcla de 3-{[(4-{[(5-amino-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (322 mg) sintetizado en el Ejemplo A110(5), benzaldehído (100 µL) y etanol (10 mL) se añadieron ácido acético (56 µL) y cianoborohidruro de sodio (61,6 mg) y la mezcla se agitó a temperatura ambiente durante 1,5 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por

1498

cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (354 mg, 93%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,37 (m, 8 H), 1,47 - 1,96 (m, 5 H), 2,01 - 2,12 (m, 1 H), 2,17 (s, 3 H), 2,56 - 2,67 (m, 2 H), 3,02 (s, 3 H), 3,66 - 3,77 (m, 3 H), 4,06 - 4,18 (m, 2 H), 4,29 - 4,39 (m, 4 H), 6,51 - 6,64 (m, 4 H), 7,14 - 7,43 (m, 8 H).

(2) ácido 3-[{[4-({[5-(bencilamino)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoico

A una mezcla de 3-[{[4-({[5-(bencilamino)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (354 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 1,5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (310 mg, 92%) en forma de un sólido blanco.

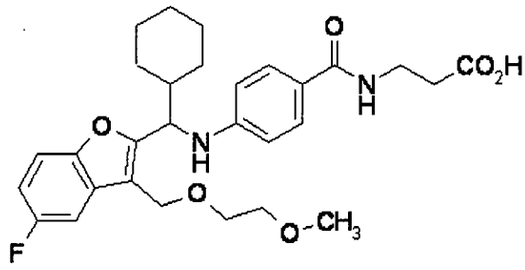
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,34 (m, 5 H), 1,47 - 1,58 (m, 1 H), 1,60 - 1,97 (m, 4 H), 2,01 - 2,12 (m, 1 H), 2,17 (s, 3 H), 2,67 (t, J = 6,4 Hz, 2 H), 3,04 (s, 3 H), 3,65 - 3,73 (m, 2 H), 4,30 - 4,36 (m, 3 H), 6,55 (d, J = 8,7 Hz, 2

1499

H), 6,59 (dd, J = 8,7, 2,7 Hz, 1 H), 6,63 - 6,67 (m, 1 H), 7,17 (d, J = 8,7 Hz, 1 H), 7,20 - 7,42 (m, 7 H).

Ejemplo A132

Ácido 3-[({4-[(ciclohexil{5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoico




(1) 5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-carboxilato de metilo

A una solución (25 mL) de 2-metoxietanol (2,74 mL) en N,N-dimetilformamida se añadió hidruro de sodio (60%, oleoso, 835 mg) a 0 °C y la mezcla se agitó a temperatura ambiente durante 30 min. Tras agitar, una solución (25 mL) de 3-(bromometil)-5-fluoro-1-benzofuran-2-carboxilato de metilo (5,00 g) sintetizada en el Ejemplo A47(2) en N,N-dimetilformamida se añadió a 0 °C. La mezcla de reacción se agitó a 80 °C durante 5 h, luego se añadió solución acuosa saturada de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 40% de acetato de etilo/hexano) para

1500

dar el compuesto objeto del título (1,54 g, 31%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,40 (s, 3 H), 3,57 - 3,62 (m, 2 H), 3,66 - 3,72 (m, 2 H), 3,99 (s, 3 H), 5,11 (s, 2 H), 7,14 - 7,22 (m, 1 H), 7,45 - 7,51 (m, 1 H), 7,60 - 7,65 (m, 1 H).

(2){5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metanol

A una mezcla de 5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-carboxilato de metilo (1,54 g) sintetizado con anterioridad, cloruro de calcio (1,21 g), etanol (15 mL) y tetrahidrofurano (15 mL) se añadió borohidruro de sodio (825 mg) a 0 °C y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (1,34 g, 97%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,38 (s, 3 H), 3,55 - 3,60 (m, 2 H), 3,63 - 3,68 (m, 2 H), 4,73 (s, 2 H), 4,76 (br s, 2 H), 6,95 - 7,04 (m, 1 H), 7,17 - 7,23 (m, 1 H), 7,33 - 7,40 (m, 1 H).

(3) 5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-carbaldehído

A una mezcla de {5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metanol (2,65 g) sintetizado con anterioridad, N-óxido de 4-metilmorfolina (2,44 g) y acetonitrilo (50 mL) se añadió perrutenato de

tetrapropilamonio (366 mg) y la mezcla se agitó durante 5 h y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 30% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,33 g, 51%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 3,41 (s, 3 H), 3,58 - 3,64 (m, 2 H), 3,72 - 3,77 (m, 2 H), 5,07 (s, 2 H), 7,21 - 7,29 (m, 1 H), 7,48 - 7,57 (m, 2 H), 10,09 (s, 1 H).

(4) ciclohexil{5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metanona

A una solución (20 mL) de 5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-carbaldehído (1,33 g) sintetizado con anterioridad en tetrahidrofurano se añadió una solución 1,0 M (7,91 mL) de bromuro de ciclohexilmagnesio en tetrahidrofurano a 0 °C y la mezcla se agitó durante 2 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 40% de acetato de etilo/hexano) para dar un aceite de color amarillo pálido. A una mezcla del aceite obtenido, N-óxido de 4-metilmorfolina (933 mg) y acetonitrilo (20 mL) se añadió perrutenato de tetrapropilamonio (140 mg) y la mezcla se agitó durante la noche a temperatura ambiente y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 20% de acetato de etilo/hexano) para

1502

dar el compuesto objeto del título (881 mg, 50%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,17 - 1,55 (m, 5 H), 1,70 - 1,80 (m, 1 H), 1,80 - 2,01 (m, 4 H), 3,24 - 3,37 (m, 1 H), 3,40 (s, 3 H), 3,57 - 3,63 (m, 2 H), 3,66 - 3,72 (m, 2 H), 5,11 (s, 2 H), 7,14 - 7,23 (m, 1 H), 7,41 - 7,48 (m, 1 H), 7,64 - 7,70 (m, 1 H).

(5) 4-[(ciclohexil{5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metil)amino]benzoato de metilo

A una mezcla de ciclohexil{5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metanona (881 mg) sintetizada con anterioridad, 4-aminobenzoato de metilo (440 mg), trietilamina (2,93 mL) y cloruro de metileno (10 mL) se añadió una solución 1,0 M (3,16 mL) de cloruro de titanio (IV) en cloruro de metileno y la mezcla se agitó bajo una atmósfera de argón durante la noche a temperatura ambiente. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido marrón oscuro. A una solución (10 mL) del sólido obtenido en tetrahidrofurano se añadieron ácido acético (301 µL) y cianoborohidruro de sodio (331 mg) y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó

1503

sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 40% de acetato de etilo/hexano) para dar el compuesto objéto del título (482 mg, 39%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,96 - 1,35 (m, 5 H), 1,41 - 1,51 (m, 1 H), 1,58 - 1,85 (m, 3 H), 1,86 - 2,01 (m, 1 H), 2,01 - 2,13 (m, 1 H), 3,43 (s, 3 H), 3,53 - 3,60 (m, 2 H), 3,60 - 3,67 (m, 2 H), 3,80 (s, 3 H), 4,46 - 4,72 (m, 3 H), 4,99 (d, J = 8,8 Hz, 1 H), 6,60 (d, J = 9,0 Hz, 2 H), 6,88 - 6,98 (m, 1 H), 7,13 - 7,19 (m, 1 H), 7,27 - 7,34 (m, 1 H), 7,78 (d, J = 9,0 Hz, 2 H).

(6) ácido 4-[(ciclohexil{5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metil)amino]benzoico

A una mezcla de 4-[(ciclohexil{5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metil)amino]benzoato de metilo (482 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (5,00 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (5,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (437 mg, 93%) en forma de un sólido de color rojo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,99 - 1,35 (m, 5 H), 1,40 - 1,53 (m, 1 H), 1,59 - 1,85 (m, 3 H), 1,86 - 2,14 (m, 2 H), 3,44 (s, 3 H), 3,52 - 3,70 (m, 4 H), 4,49 - 4,73 (m, 3 H),

1504

6,62 (d, J = 8,9 Hz, 2 H), 6,91 - 7,00 (m, 1 H), 7,14 - 7,20 (m, 1 H), 7,29 - 7,36 (m, 1 H), 7,84 (d, J = 8,9 Hz, 2 H).

(7) 3-[({4-[(ciclohexil{5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoato de etilo

A una mezcla de ácido 4-[(ciclohexil{5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metil)amino]benzoico (200 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (101 mg), monohidrato de 1-hidroxibenzotriazol (101 mg), trietilamina (184 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (126 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (216 mg, 89%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 1,34 (m, 8 H), 1,41 - 1,52 (m, 1 H), 1,60 - 2,01 (m, 4 H), 2,03 - 2,13 (m, 1 H), 2,58 (t, J = 5,9 Hz, 2 H), 3,43 (s, 3 H), 3,54 - 3,69 (m, 6 H), 4,13 (q, J = 7,1 Hz, 2 H), 4,45 - 4,53 (m, 1 H), 4,57 (d, J = 12,1 Hz, 1 H), 4,65 (d, J = 12,1 Hz, 1 H), 4,87 (d, J = 8,5 Hz, 1 H), 6,56 - 6,65 (m, 3 H), 6,88 - 6,98 (m, 1 H),

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7,14 - 7,20 (m, 1 H), 7,28 - 7,34 (m, 1 H), 7,53 (d, J = 8,8 Hz, 2 H).

(8) ácido 3-[({4-[(ciclohexil{5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoico

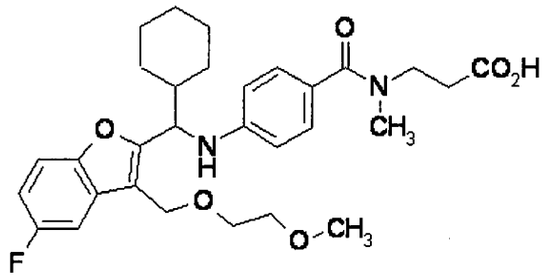
A una mezcla de 3-[({4-[(ciclohexil{5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoato de etilo (216 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 3 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (69,6 mg, 34%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,99 - 1,35 (m, 5 H), 1,40 - 1,51 (m, 1 H), 1,59 - 1,85 (m, 3 H), 1,84 - 2,00 (m, 1 H), 2,01 - 2,12 (m, 1 H), 2,63 (t, J = 5,7 Hz, 2 H), 3,42 (s, 3 H), 3,54 - 3,69 (m, 6 H), 4,49 (d, J = 8,3 Hz, 1 H), 4,56 (d, J = 12,1 Hz, 1 H), 4,64 (d, J = 12,1 Hz, 1 H), 6,53 - 6,67 (m, 3 H), 6,88 - 6,99 (m, 1 H), 7,12 - 7,20 (m, 1 H), 7,27 - 7,34 (m, 1 H), 7,52 (d, J = 8,7 Hz, 2 H).

Ejemplo A133

Ácido 3-[({4-[(ciclohexil{5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

1506



(1) 3-[({4-[(ciclohexil{5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo

A una mezcla de ácido 4-[(ciclohexil{5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metil)amino]benzoico (200 mg) sintetizado en el Ejemplo A132(6), 3-(metilamino)propanoato de etilo (86,4 mg), monohidrato de 1-hidroxibenzotriazol (101 mg), trietilamina (184 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (126 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (175 mg, 70%) en forma de un aceite de color marrón pálido.

1507

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 1,37 (m, 8 H), 1,42 - 1,53 (m, 1 H), 1,59 - 2,00 (m, 4 H), 2,03 - 2,14 (m, 1 H), 2,61 (t, J = 7,0 Hz, 2 H), 3,01 (s, 3 H), 3,42 (s, 3 H), 3,54 - 3,75 (m, 6 H), 4,11 (q, J = 7,1 Hz, 2 H), 4,42 - 4,51 (m, 1 H), 4,59 (d, J = 12,1 Hz, 1 H), 4,65 (d, J = 12,1 Hz, 1 H), 4,71 (d, J = 8,5 Hz, 1 H), 6,59 (d, J = 8,8 Hz, 2 H), 6,89 - 6,98 (m, 1 H), 7,16 - 7,23 (m, 3 H), 7,28 - 7,34 (m, 1 H).

(2) ácido 3-[({4-[(ciclohexil{5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

A una mezcla de 3-[({4-[(ciclohexil{5-fluoro-3-[(2-metoxietoxi)metil]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo (175 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL), ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (143 mg, 82%) en forma de un sólido amarillo.

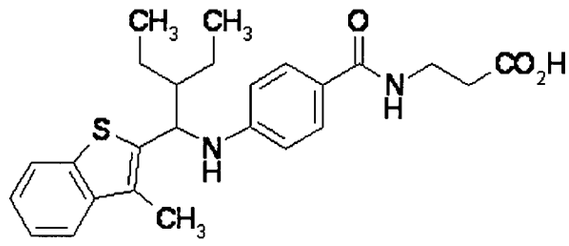
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,99 - 1,35 (m, 5 H), 1,40 - 1,51 (m, 1 H), 1,60 - 2,00 (m, 4 H), 2,02 - 2,15 (m, 1 H), 2,64 (t, J = 6,4 Hz, 2 H), 3,02 (s, 3 H), 3,42 (s, 3 H), 3,54 - 3,75 (m, 6 H), 4,47 (d, J = 8,3 Hz, 1 H), 4,59 (d, J = 12,3 Hz, 1 H), 4,66 (d, J = 12,3 Hz, 1 H), 6,60 (d, J = 8,7 Hz, 2

1508

H), 6,89 - 6,99 (m, 1 H), 7,16 - 7,25 (m, 3 H), 7,28 - 7,35 (m, 1 H).

Ejemplo A134

Ácido 3-{[(4-{[2-etil-1-(3-metil-1-benzotiofen-2-il)butil]amino}fenil)carbonil]amino}propanoico



(1) 2-etil-1-(3-metil-1-benzotiofen-2-il)butan-1-ona

A una mezcla de 3-metil-1-benzotiofeno (1,00 g), cloruro de 2-etilbutirilo (1,02 mL) y nitrometano (10 mL) se añadió cloruro de aluminio (1,35 g) a 0 °C y la mezcla se agitó durante 3 h. Se añadió agua para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 10% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,65 g, 99%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 (t, J = 7,4 Hz, 6 H), 1,51 - 1,67 (m, 2 H), 1,75 - 1,92 (m, 2 H), 2,78 (s, 3 H), 2,97 - 3,08 (m, 1 H), 7,40 - 7,53 (m, 2 H), 7,81 - 7,91 (m, 2 H).

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(2) 4-{[2-etil-1-(3-metil-1-benzotiofen-2-il)butil]amino}benzoato de metilo

A una mezcla de 2-etil-1-(3-metil-1-benzotiofen-2-il)butan-1-ona (1,65 g) sintetizada con anterioridad, 4-aminobenzoato de metilo (1,15 g), trietilamina (7,47 mL) y cloruro de metileno (15 mL) se añadió una solución 1,0 M (8,04 mL) de cloruro de titanio (IV) en cloruro de metileno y la mezcla se agitó bajo una atmósfera de argón durante la noche a temperatura ambiente. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción, el cloruro de metileno se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una mezcla del aceite obtenido, 4-aminobenzoato de metilo (506 mg), trietilamina (7,47 mL) y cloruro de metileno (30 mL) se añadió cloruro de titanio (IV) (882 µL) y la mezcla se agitó bajo una atmósfera de argón durante la noche a temperatura ambiente. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (30 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (797 µL) y cianoborohidruro de sodio (842 mg) y la mezcla se agitó a temperatura ambiente durante 1,5 h. Se añadió solución saturada acuosa de hidrógeno-carbonato de

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sodio para neutralizar la reacción, el solvente orgánico se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (10 - 40% de acetato de etilo/hexano) para dar el compuesto objeto del título (580 mg, 23%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 - 0,99 (m, 6 H), 1,33 - 1,56 (m, 3 H), 1,67 - 1,84 (m, 2 H), 2,46 (s, 3 H), 3,79 (s, 3 H), 4,45 (d, J = 6,6 Hz, 1 H), 4,81 - 4,89 (m, 1 H), 6,52 (d, J = 9,0 Hz, 2 H), 7,22 - 7,29 (m, 1 H), 7,31 - 7,38 (m, 1 H), 7,61 - 7,66 (m, 1 H), 7,67 - 7,71 (m, 1 H), 7,77 (d, J = 9,0 Hz, 2 H).

(3) ácido 4-{[2-etil-1-(3-metil-1-benzotiofen-2-il)butil]amino}benzoico

A una mezcla de 4-{[2-etil-1-(3-metil-1-benzotiofen-2-il)butil]amino}benzoato de metilo (580 mg) sintetizado con anterioridad, tetrahidrofurano (10 mL) y etanol (10 mL) se añadió solución acuosa 1 N de hidróxido de sodio (10,0 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (20 mL) y ácido clorhídrico 1 N (10,0 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (529 mg, 95%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,87 - 0,99 (m, 6 H), 1,32 - 1,56 (m, 3 H), 1,67 - 1,83 (m, 2 H), 2,46 (s, 3 H), 4,46 -

4,54 (m, 1 H), 4,82 - 4,91 (m, 1 H), 6,53 (d, J = 8,7 Hz, 2 H), 7,22 - 7,30 (m, 1 H), 7,32 - 7,39 (m, 1 H), 7,65 (d, J = 7,6 Hz, 1 H), 7,70 (d, J = 7,6 Hz, 1 H), 7,81 (d, J = 8,7 Hz, 2 H).

(4) 3-{[(4-{[2-etil-1-(3-metil-1-benzotiofen-2-il)butil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[2-etil-1-(3-metil-1-benzotiofen-2-il)butil]amino}benzoico (250 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (157 mg), monohidrato de 1-hidroxibenzotriazol (156 mg), trietilamina (284 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (196 mg) y la mezcla se agitó a temperatura ambiente durante 2,5 días. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (330 mg, cuantitativo) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 - 0,97 (m, 6 H), 1,24 (t, J = 7,1 Hz, 3 H), 1,33 - 1,55 (m, 3 H), 1,67 - 1,83 (m, 2 H), 2,46 (s, 3 H), 2,54 - 2,60 (m, 2 H), 3,60 - 3,68 (m, 2 H), 4,12 (q, J = 7,1 Hz, 2 H), 4,35 (d, J = 6,6 Hz, 1 H), 4,79 - 4,86 (m, 1 H), 6,50 - 6,61 (m, 3 H), 7,22 - 7,29 (m, 1 H),

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7,31 - 7,37 (m, 1 H), 7,52 (d, J = 8,5 Hz, 2 H), 7,61 - 7,66 (m, 1 H), 7,66 - 7,71 (m, 1 H).

(5) ácido 3-{[(4-{[2-etil-1-(3-metil-1-benzotiofen-2-il)butil]amino}fenil)carbonil]amino}propanoico

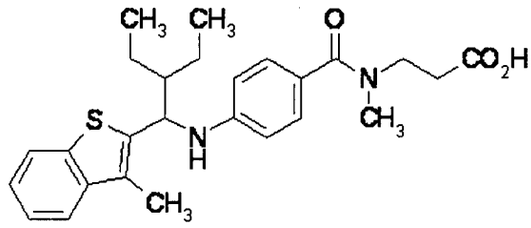
A una mezcla de 3-{[(4-{[2-etil-1-(3-metil-1-benzotiofen-2-il)butil]amino}fenil)carbonil]amino}propanoato de etilo (330 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (272 mg, 91%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 - 0,97 (m, 6 H), 1,32 - 1,56 (m, 3 H), 1,66 - 1,83 (m, 2 H), 2,45 (s, 3 H), 2,60 (t, J = 5,5 Hz, 2 H), 3,57 - 3,66 (m, 2 H), 4,82 (d, J = 6,0 Hz, 1 H), 6,47 - 6,58 (m, 3 H), 7,22 - 7,29 (m, 1 H), 7,31 - 7,38 (m, 1 H), 7,50 (d, J = 8,7 Hz, 2 H), 7,64 (d, J = 7,5 Hz, 1 H), 7,69 (d, J = 7,9 Hz, 1 H).

Ejemplo A135

Ácido 3-{[(4-{[2-etil-1-(3-metil-1-benzotiofen-2-il)butil]amino}fenil)carbonil](metil)amino}propanoico

1513



(1) 3-{[(4-{[2-etil-1-(3-metil-1-benzotiofen-2-il)butil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[2-etil-1-(3-metil-1-benzotiofen-2-il)butil]amino}benzoico (250 mg) sintetizado en el Ejemplo A134(3), 3-(metilamino)propanoato de etilo (134 mg), monohidrato de 1-hidroxibenzotriazol (156 mg), trietilamina (284 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (196 mg) y la mezcla se agitó a temperatura ambiente 2,5 días. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada y solución acuosa saturada de carbonato ácido de sodio, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (253 mg, 77%) en forma de un aceite incoloro. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,87 - 0,97 (m, 6 H), 1,22 (t, J = 7,1 Hz, 3 H), 1,32 - 1,54 (m, 3 H), 1,67 - 1,82 (m, 2 H), 2,45 (s, 3 H), 2,60 (t, J = 7,0 Hz, 2 H), 3,00 (s, 3 H), 3,69

(t, J = 7,0 Hz, 2 H), 4,10 (q, J = 7,1 Hz, 2 H), 4,23 (d, J = 6,3 Hz, 1 H), 4,76 - 4,83 (m, 1 H), 6,51 (d, J = 8,8 Hz, 2 H), 7,19 (d, J = 8,8 Hz, 2 H), 7,22 - 7,29 (m, 1 H), 7,31 - 7,38 (m, 1 H), 7,61 - 7,66 (m, 1 H), 7,68 - 7,72 (m, 1 H).

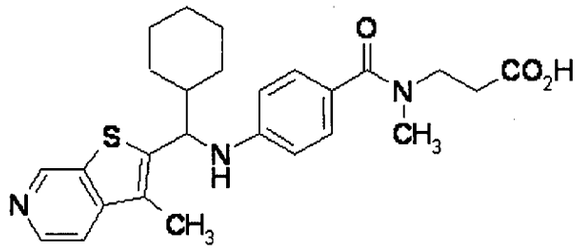
(2) ácido 3-{[(4-{[2-etil-1-(3-metil-1-benzotiofen-2-il)butil]amino}fenil)carbonil](metil)amino}propanoico

A una mezcla de 3-{[(4-{[2-etil-1-(3-metil-1-benzotiofen-2-il)butil]amino}fenil)carbonil](metil)amino}propanoato de etilo (253 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (225 mg, 95%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,84 - 0,99 (m, 6 H), 1,30 - 1,56 (m, 3 H), 1,66 - 1,81 (m, 2 H), 2,45 (s, 3 H), 2,64 (t, J = 6,4 Hz, 2 H), 3,01 (s, 3 H), 3,68 (t, J = 6,4 Hz, 2 H), 4,80 (d, J = 6,4 Hz, 1 H), 6,52 (d, J = 8,7 Hz, 2 H), 7,21 (d, J = 8,7 Hz, 2 H), 7,23 - 7,30 (m, 1 H), 7,31 - 7,38 (m, 1 H), 7,64 (d, J = 7,9 Hz, 1 H), 7,71 (d, J = 7,5 Hz, 1 H).

Ejemplo A136

Ácido 3-{[(4-{[ciclohexil(3-metiltieno[2,3-c]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

1515



(1) 3-metiltieno[2,3-c]piridin-2-carboxilato de etilo

A una solución (120 mL) de 3-cloropiridin-4-carbonitrilo (10,3 g) en tetrahidrofurano se añadió una solución 3,0 M (49,8 mL) de cloruro de metilmagnesio en tetrahidrofurano bajo una atmósfera de nitrógeno a 0 °C y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió agua (50 mL) a la mezcla de reacción, luego se agregó ácido sulfúrico al 10% (100 mL) a la mezcla de reacción y la mezcla se agitó durante la noche. Se agregó carbonato de sodio para acidificar la solución a pH = 9 y la mezcla se extrajo con acetato de etilo. El extracto se secó sobre sulfato de sodio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice para dar un aceite incoloro (6,10 g). A una mezcla del aceite obtenido (6,00 g), mercaptoacetato deetilo (11,6 mL) y N,N-dimetilformamida anhidra (100 mL) se añadió hidruro de sodio (60%, oleoso, 4,0 g) a 5 °C durante 30 min y la mezcla se agitó a 5 °C durante 20 min, luego a temperatura ambiente durante la noche. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción y la mezcla de reacción se vertió en agua. El sólido precipitado se recogió por

filtración y se recristalizó en éter de petróleo/acetato de etilo para dar el compuesto objeto del título (5,12 g, 31%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,42 (t, J = 7,2 Hz, 3H), 2,76 (s, 3H), 4,41 (q, J = 7,2 Hz, 2H), 7,69 (dd, J = 5,7, 0,9 Hz, 1H), 8,57 (d, J = 5,7 Hz, 1H), 9,14 (d, J = 0,6 Hz, 1H).

(2) 3-metiltieno[2,3-c]piridin-2-carbaldehído

A una mezcla de 3-metiltieno[2,3-c]piridin-2-carboxilato de etilo (2,00 g) sintetizado con anterioridad, cloruro de calcio (2,01 g), etanol (30 mL) y tetrahidrofurano (30 mL) se añadió borohidruro de sodio (1,37 g) a 0 °C y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido de color amarillo pálido. A una solución (40 mL) del sólido obtenido en tetrahidrofurano se añadió dióxido de manganeso activo (8,10 g) y la mezcla se agitó a 50 °C durante 8 h. El dióxido de manganeso se filtró y el filtrado se concentró a presión reducida para dar el compuesto objeto del título (1,39 g, 87%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,81 (s, 3 H), 7,75 (dd, J = 5,5, 1,1 Hz, 1 H), 8,61 (d, J = 5,5 Hz, 1 H), 9,20 (d, J = 1,1 Hz, 1 H), 10,41 (s, 1 H).

(3) ciclohexil(3-metiltieno[2,3-c]piridin-2-il)metanona

1517

A una solución (30 mL) de 3-metiltieno[2,3-c]piridin-2-carbaldehído (1,39 g) sintetizado con anterioridad en tetrahidrofurano se añadió una solución 1,0 M (15,7 mL) de bromuro de ciclohexilmagnesio en tetrahidrofurano a 0 °C y la mezcla se agitó durante 1,5 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción, el tetrahidrofurano se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar un sólido de color amarillo pálido. A una mezcla del sólido obtenido, N-óxido de 4-metilmorfolina (680 mg) y acetonitrilo (20 mL) se añadió perrutenato de tetrapropilamonio (113 mg) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 40% de acetato de etilo/hexano) para dar el compuesto objeto del título (628 mg, 31%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,22 - 1,62 (m, 5 H), 1,70 - 1,81 (m, 1 H), 1,82 - 1,94 (m, 2 H), 1,95 - 2,06 (m, 2 H), 2,73 (s, 3 H), 2,97 - 3,09 (m, 1 H), 7,71 (dd, J = 5,5, 1,1 Hz, 1 H), 8,58 (d, J = 5,5 Hz, 1 H), 9,16 (d, J = 1,1 Hz, 1 H).

(4) ácido 4-{[ciclohexil(3-metilfuro[2,3-c]piridin-2-il)metil]amino}benzoico

1578

A una mezcla de ciclohexil(3-metiltieno[2,3-c]piridin-2-il)metanona (628 mg) sintetizado con anterioridad, 4-aminobenzoato de metilo (402 mg), trietilamina (2,70 mL) y cloruro de metileno (10 mL) se añadió cloruro de titanio (IV) (318 µL) y la mezcla se agitó bajo una atmósfera de argón durante la noche a temperatura ambiente. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (30 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (277 µL) y cianoborohidruro de sodio (304 mg) y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción, el solvente orgánico se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar un sólido anaranjado. A una mezcla del sólido obtenido, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (5,00 mL) y la mezcla se agitó con calentamiento a reflujo durante 4 h. Se añadió ácido clorhídrico 1 N (5,00 mL) a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se

concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (40 - 100% de acetato de etilo/hexano) para dar el compuesto objeto del título (202 mg, 22%) en forma de un sólido amarillo. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,07 - 1,34 (m, 5 H), 1,40 - 1,93 (m, 5 H), 2,01 - 2,16 (m, 1 H), 2,50 (s, 3 H), 4,58 - 4,69 (m, 2 H), 6,51 (d, J = 8,8 Hz, 2 H), 7,52 (dd, J = 5,6, 0,9 Hz, 1 H), 7,82 (d, J = 8,8 Hz, 2 H), 8,49 (d, J = 5,6 Hz, 1 H), 8,95 (d, J = 0,9 Hz, 1 H).

(5) 3-{[(4-{[ciclohexil(3-metiltieno[2,3-c]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclohexil(3-metilfuro[2,3-c]piridin-2-il)metil]amino}benzoico (202 mg) sintetizado con anterioridad, 3-(metilamino)propanoato de etilo (104 mg), monohidrato de 1-hidroxibenzotriazol (122 mg), trietilamina (222 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (152 mg) y la mezcla se agitó a temperatura ambiente durante 1 día. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 100% de acetato de etilo/hexano, ten 0 - 10% metanol/acético) para dar el

1520

compuesto objeto del título (151 mg, 58%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,06 - 1,36 (m, 8 H), 1,53 - 1,88 (m, 5 H), 2,03 - 2,16 (m, 1 H), 2,48 (s, 3 H), 2,60 (t, J = 7,0 Hz, 2 H), 2,99 (s, 3 H), 3,69 (t, J = 7,0 Hz, 2 H), 4,10 (q, J = 7,1 Hz, 2 H), 4,35 (d, J = 5,7 Hz, 1 H), 4,58 (dd, J = 7,3, 5,7 Hz, 1 H), 6,49 (d, J = 8,7 Hz, 2 H), 7,19 (d, J = 8,7 Hz, 2 H), 7,51 (dd, J = 5,7, 1,1 Hz, 1 H), 8,48 (d, J = 5,7 Hz, 1 H), 8,95 (d, J = 1,1 Hz, 1 H).

(6) ácido 3-{[(4-{[ciclohexil(3-metiltieno[2,3-c]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

A una mezcla de 3-{[(4-{[ciclohexil(3-metiltieno[2,3-c]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (151 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 5 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (80,2 mg, 56%) en forma de un sólido blanco.

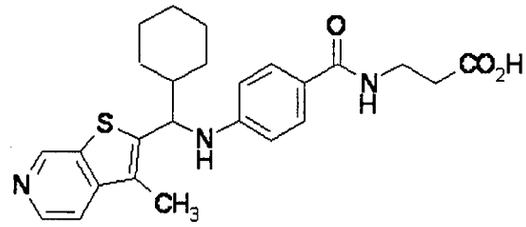
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,04 - 1,34 (m, 5 H), 1,50 - 1,62 (m, 1 H), 1,63 - 1,88 (m, 4 H), 2,02 - 2,14 (m, 1 H), 2,48 (s, 3 H), 2,53 - 2,68 (m, 2 H), 3,00 (s, 3 H), 3,58 - 3,74 (m, 2 H), 4,57 (d, J = 7,5 Hz, 1 H), 6,47 (d, J = 8,5

1521

Hz, 2 H), 7,19 (d, J = 8,5 Hz, 2 H), 7,55 (d, J = 5,7 Hz, 1 H), 8,43 (d, J = 5,7 Hz, 1 H), 8,94 (s, 1 H).

Ejemplo A137

Ácido 3-{[(4-{[ciclohexil(3-metiltieno[2,3-c]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoico



(1) 3-{[(4-{[ciclohexil(3-metiltieno[2,3-c]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclohexil(3-metilfuro[2,3-c]piridin-2-il)metil]amino}benzoico (201 mg) sintetizado en el Ejemplo A136(4), clorhidrato de éster etílico de β-alanina (122 mg), monohidrato de 1-hidroxibenzotriazol (121 mg), trietilamina (220 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (152 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de

1522

sílice (60 - 100% de acetato de etilo/hexano) para dar el compuesto objeto del título (209 mg, 83%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,06 - 1,37 (m, 8 H), 1,53 - 1,89 (m, 5 H), 2,05 - 2,16 (m, 1 H), 2,48 (s, 3 H), 2,56 (t, J = 5,8 Hz, 2 H), 3,59 - 3,68 (m, 2 H), 4,12 (q, J = 7,1 Hz, 2 H), 4,50 (d, J = 5,8 Hz, 1 H), 4,58 - 4,64 (m, 1 H), 6,50 (d, J = 8,8 Hz, 2 H), 6,61 (t, J = 5,9 Hz, 1 H), 7,51 (dd, J = 5,5, 1,1 Hz, 1 H), 7,52 (d, J = 8,8 Hz, 2 H), 8,47 (d, J = 5,5 Hz, 1 H), 8,93 (d, J = 1,1 Hz, 1 H).

(2) ácido 3-{[(4-{[ciclohexil(3-metiltieno[2,3-c]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoico

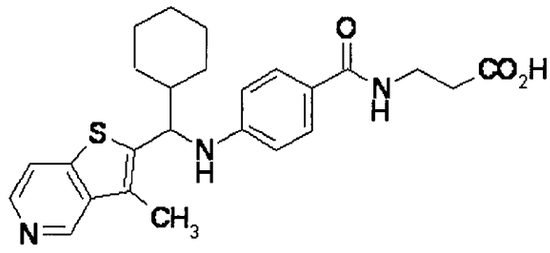
A una mezcla de 3-{[(4-{[ciclohexil(3-metiltieno[2,3-c]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo (209 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (169 mg, 86%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,04 - 1,36 (m, 5 H), 1,49 - 1,89 (m, 5 H), 2,02 - 2,14 (m, 1 H), 2,48 (s, 3 H), 2,59 (t, J = 5,7 Hz, 2 H), 3,51 - 3,77 (m, 2 H), 4,59 (d, J = 7,2 Hz, 1 H), 6,47 (d, J = 8,7 Hz, 2 H), 6,85 (t, J = 5,8 Hz, 1 H), 7,48 - 7,60 (m, 3 H), 8,42 (d, J = 5,7 Hz, 1 H), 8,88 (s, 1 H).

1523

Ejemplo A138

Ácido 3-{[(4-{[ciclohexil(3-metiltieno[3,2-c]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoico




(1) 3-metiltieno[3,2-c]piridin-2-carboxilato de etilo

El cloruro de tionilo (100 mL) se añadió a ácido 4-cloronicotínico (22,4 g) y la mezcla se agitó con calentamiento a reflujo durante 4 h y se concentró a presión reducida. A una solución (300 mL) del residuo en cloruro de metileno se añadieron clorhidrato de N,O-dimetilhidroxilamina (13,8 g) y trietilamina (60 mL) y la mezcla se agitó a temperatura ambiente durante 5 h. Se añadió agua a la mezcla de reacción y la mezcla de reacción se extrajo con cloruro de metileno. El extracto se secó sobre sulfato de sodio y se concentró a presión reducida. A una solución (300 mL) del residuo en tetrahidrofurano se añadió una solución 3,0 M (54 mL) de cloruro de metilmagnesio en éter a -78 °C y la mezcla se agitó bajo una atmósfera de nitrógeno a temperatura ambiente durante 10 h. La mezcla de reacción se acidificó con una solución acuosa de carbonato de sodio a pH = 9 y se extrajo con acetato de etilo. El extracto se secó sobre sulfato de sodio y se concentró a presión reducida para dar

1524

un aceite incoloro. A una mezcla del aceite obtenido, mercaptoacetato de etilo (21 mL) y N,N-dimetilformamida anhidra (200 mL) se añadió hidruro de sodio (60%, oleoso, 7,34 g) a 5 °C durante 30 min y la mezcla se agitó a 5 °C durante 20 min, luego a temperatura ambiente durante 18 h. Se añadió agua para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se secó sobre sulfato de sodio y se concentró a presión reducida. El sólido obtenido se recristalizó en éter de petróleo/acetato de etilo para dar el compuesto objeto del título (5,45 g, 17%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,43 (t, J = 7,2 Hz, 3H), 2,85 (s, 3H), 4,42 (q, J = 7,2 Hz, 2H), 7,74 (dd, J = 5,7, 0,9 Hz, 1H), 8,55 (d, J = 6,0 Hz, 1H), 9,14 (d, J = 1,2 Hz, 1H).

(2) 3-metiltieno[3,2-c]piridin-2-carbaldehído

A una mezcla de 3-metiltieno[3,2-c]piridin-2-carboxilato de etilo (3,40 g) sintetizado con anterioridad, cloruro de calcio (3,42 g), etanol (30 mL) y tetrahidrofurano (30 mL) se añadió borohidruro de sodio (2,33 g) a 0 °C y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color amarillo pálido. A una solución (60 mL) del aceite obtenido en tetrahidrofurano se añadió dióxido de manganeso activo (14,4 g) y la mezcla se agitó a 50 °C durante la noche. El dióxido de manganeso se filtró y

1525

el filtrado se concentró a presión reducida. El residuo se lavó con éter diisopropílico para dar el compuesto objeto del título (1,54 g, 56%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,89 (s, 3 H), 7,79 (dd, J = 5,5, 0,8 Hz, 1 H), 8,58 (d, J = 5,5 Hz, 1 H), 9,21 (d, J = 0,8 Hz, 1 H), 10,35 (s, 1 H).

(3) ciclohexil(3-metiltieno[3,2-c]piridin-2-il)metanona

A una solución (40 mL) de 3-metiltieno[3,2-c]piridin-2-carbaldehído (1,87 g) sintetizado con anterioridad en tetrahidrofurano se añadió una solución 1,0 M (21,2 mL) de bromuro de ciclohexilmagnesio en tetrahidrofurano a 0 °C y la mezcla se agitó durante 1 h. Una solución 1,0 M (10,0 mL) de bromuro de ciclohexilmagnesio en tetrahidrofurano se añadió además y la mezcla luego se agitó a 0 °C durante 1 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 90% de acetato de etilo/hexano) para dar un sólido de color amarillo pálido. A una mezcla del sólido obtenido, N-óxido de 4-metilmorfolina (1,24 mg) y acetonitrilo (30 mL) se añadió perrutenato de tetrapropilamonio (164 mg) y la mezcla se agitó a temperatura ambiente durante 4 h y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (10 - 50% de acetato de etilo/hexano) para dar el

(526

compuesto objeto del título (864 mg, 31%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,19 - 1,61 (m, 5 H), 1,69 - 1,80 (m, 1 H), 1,81 - 1,92 (m, 2 H), 1,93 - 2,04 (m, 2 H), 2,82 (s, 3 H), 2,93 - 3,05 (m, 1 H), 7,75 (dd, J = 5,7, 1,0 Hz, 1 H), 8,55 (d, J = 5,7 Hz, 1 H), 9,17 (d, J = 1,0 Hz, 1 H).

(4) ácido 4-{[ciclohexil(3-metilfuro[3,2-c]piridin-2-il)metil]amino}benzoico

A una mezcla de ciclohexil(3-metiltieno[3,2-c]piridin-2-il)metanona (864 mg) sintetizada con anterioridad, 4-aminobenzoato de metilo (553 mg), trietilamina (3,71 mL) y cloruro de metileno (20 mL) se añadió cloruro de titanio (IV) (439 µL) a 0 °C y la mezcla se agitó bajo una atmósfera de argón durante la noche a temperatura ambiente. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (20 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (268 µL) y cianoborohidruro de sodio (419 mg) y la mezcla se agitó a temperatura ambiente durante 1,5 h. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se

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purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar un sólido de color marrón pálido. A una mezcla del sólido obtenido, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (5,00 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo. Tetrahidrofurano (5 mL), etanol (5 mL) y solución acuosa 1 N de hidróxido de sodio (5,00 mL) se agregaron adicionalmente y la mezcla se agitó con calentamiento a reflujo durante 2,5 h y se añadió etilendiamina (1,00 mL). La mezcla se agitó con calentamiento a reflujo durante 4 h y se concentró a presión reducida. El residuo se acidificó con ácido clorhídrico 1 N hasta pH = 4 y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (50 - 100% de acetato de etilo/hexano) para dar el compuesto objeto del título (432 mg, 34%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,04 - 1,37 (m, 5 H), 1,53 - 1,90 (m, 5 H), 2,03 - 2,15 (m, 1 H), 2,56 (s, 3 H), 4,55 - 4,66 (m, 2 H), 6,51 (d, J = 8,7 Hz, 2 H), 7,63 (dd, J = 5,5, 1,1 Hz, 1 H), 7,84 (d, J = 8,7 Hz, 2 H), 8,39 (d, J = 5,5 Hz, 1 H), 8,97 (d, J = 1,1 Hz, 1 H).

(5) 3-{[(4-{[ciclohexil(3-metiltieno[3,2-c]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclohexil(3-metilfuro[3,2-c]piridin-2-il)metil]amino}benzoico (211 mg) sintetizado con

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anterioridad, clorhidrato de éster etílico de β-alanina (128 mg), monohidrato de 1-hidroxibenzotriazol (128 mg), trietilamina (233 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (160 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (60 - 100% de acetato de etilo/hexano) para dar el compuesto objeto del título (214 mg, 80%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,05 - 1,37 (m, 8 H), 1,53 - 1,91 (m, 5 H), 2,04 - 2,16 (m, 1 H), 2,50 - 2,63 (m, 5 H), 3,58 - 3,70 (m, 2 H), 4,12 (q, J = 7,1 Hz, 2 H), 4,42 (d, J = 5,8 Hz, 1 H), 4,52 - 4,62 (m, 1 H), 6,51 (d, J = 8,7 Hz, 2 H), 6,59 (t, J = 5,8 Hz, 1 H), 7,52 (d, J = 8,7 Hz, 2 H), 7,60 (d, J = 5,5 Hz, 1 H), 8,37 (d, J = 5,5 Hz, 1 H), 8,93 (s, 1 H).

(6) ácido 3-{[(4-{[ciclohexil(3-metiltieno[3,2-c]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoico

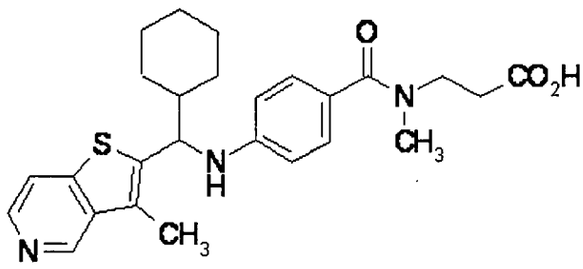
A una mezcla de 3-{[(4-{[ciclohexil(3-metiltieno[3,2-c]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo (186 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de

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hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (186 mg, 93%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,05 - 1,36 (m, 5 H), 1,55 - 1,64 (m, 1 H), 1,65 - 1,90 (m, 4 H), 2,03 - 2,15 (m, 1 H), 2,56 (s, 3 H), 2,61 (t, J = 5,1 Hz, 2 H), 3,52 - 3,67 (m, 1 H), 3,73 - 3,89 (m, 1 H), 4,56 (d, J = 7,2 Hz, 1 H), 6,48 (d, J = 8,7 Hz, 2 H), 6,89 - 6,99 (m, 1 H), 7,58 (d, J = 8,7 Hz, 2 H), 7,69 (d, J = 5,7 Hz, 1 H), 8,31 (d, J = 5,7 Hz, 1 H), 8,96 (s, 1 H).

Ejemplo A139

Ácido 3-{[(4-{[ciclohexil(3-metiltieno[3,2-c]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) 3-{[(4-{[ciclohexil(3-metiltieno[3,2-c]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

1530

A una mezcla de ácido 4-{[ciclohexil(3-metilfuro[3,2-c]piridin-2-il)metil]amino}benzoico (209 mg) sintetizado en el Ejemplo A138(4), 3-(metilamino)propanoato de etilo (108 mg), monohidrato de 1-hidroxibenzotriazol (126 mg), trietilamina (229 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (158 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (60 - 100% de acetato de etilo/hexano, luego 0 - 10% de metanol/acetato de etilo) para dar el compuesto objeto del título (180 mg, 66%) en forma de un aceite incoloro.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,04 - 1,38 (m, 8 H), 1,52 - 1,94 (m, 5 H), 2,02 - 2,16 (m, 1 H), 2,55 (s, 3 H), 2,60 (t, J = 6,9 Hz, 2 H), 2,99 (s, 3 H), 3,69 (t, J = 6,9 Hz, 2 H), 4,10 (q, J = 6,8 Hz, 2 H), 4,27 - 4,39 (m, 1 H), 4,49 - 4,59 (m, 1 H), 6,49 (d, J = 8,5 Hz, 2 H), 7,19 (d, J = 8,5 Hz, 2 H), 7,62 (d, J = 5,5 Hz, 1 H), 8,38 (d, J = 5,5 Hz, 1 H), 8,93 (s, 1 H).

(2) ácido 3-{[(4-{[ciclohexil(3-metiltieno[3,2-c]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

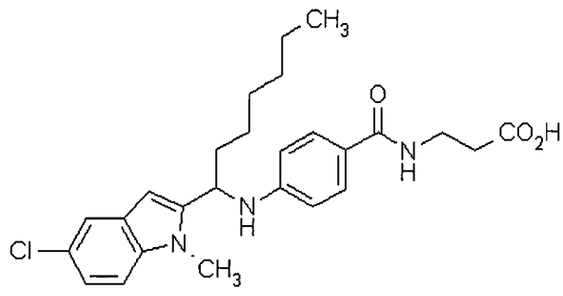
A una mezcla de 3-{[(4-{[ciclohexil(3-metiltieno[3,2-c]piridin-2-

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il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (180 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,00 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (1,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (136 mg, 80%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 - 1,32 (m, 5 H), 1,52 - 1,63 (m, 1 H), 1,63 - 1,89 (m, 4 H), 2,03 - 2,15 (m, 1 H), 2,53 (s, 3 H), 2,58 - 2,74 (m, 2 H), 3,03 (s, 3 H), 3,62 - 3,79 (m, 2 H), 4,54 (d, J = 7,5 Hz, 1 H), 6,48 (d, J = 8,7 Hz, 2 H), 7,22 (d, J = 8,7 Hz, 2 H), 7,67 (d, J = 5,5 Hz, 1 H), 8,34 (d, J = 5,5 Hz, 1 H), 8,93 (s, 1 H).

Ejemplo A140

Ácido 3-{[(4-{[1-(5-cloro-1-metil-1H-indol-2-il)heptil]amino}fenil)carbonil]amino}propanoico




(1) 1-(5-cloro-1-metil-1H-indol-2-il)heptan-1-ona

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A una solución (10 mL) de 1-(5-cloro-1H-indol-2-il)heptan-1-ona (1,00 g) sintetizada en el Ejemplo A106(2) en N,N-dimetilformamida se añadió hidruro de sodio (60%, oleoso, 182 mg) a 0 °C y la mezcla se agitó bajo una atmósfera de argón durante 30 min. Tras agitar, se añadió yoduro de metilo (354 µL). La mezcla de reacción se agitó a temperatura ambiente durante la noche, se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con hexano para dar el compuesto objeto del título (367 mg, 35%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 - 0,94 (m, 3 H), 1,24 - 1,46 (m, 6 H), 1,68 - 1,81 (m, 2 H), 2,90 - 2,98 (m, 2 H), 4,05 (s, 3 H), 7,19 (s, 1 H), 7,28 - 7,31 (m, 2 H), 7,63 - 7,66 (m, 1 H).

(2) 4-{[1-(5-cloro-1-metil-1H-indol-2-il)heptil]amino}benzoato de metilo

A una mezcla de 1-(5-cloro-1-metil-1H-indol-2-il)heptan-1-ona (1,05 g) sintetizada con anterioridad, 4-aminobenzoato de metilo (629 mg), trietilamina (4,21 mL) y cloruro de metileno (10 mL) se añadió una solución 1,0 M (4,54 mL) de cloruro de titanio (IV) en cloruro de metileno a 0 °C y la mezcla se agitó durante la noche a temperatura ambiente bajo una atmósfera de argón. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El

1533

extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido marrón oscuro. A una solución (10 mL) del sólido obtenido en tetrahidrofurano se añadieron ácido acético (1,08 mL) y cianoborohidruro de sodio (475 mg) y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 30% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,15 g, 74%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,83 - 0,91 (m, 3 H), 1,21 - 1,53 (m, 8 H), 1,88 - 2,08 (m, 2 H), 3,68 (s, 3 H), 3,83 (s, 3 H), 4,25 (d, J = 7,1 Hz, 1 H), 4,60 - 4,70 (m, 1 H), 6,37 (s, 1 H), 6,55 (d, J = 8,8 Hz, 2 H), 7,13 (dd, J = 8,7, 1,9 Hz, 1 H), 7,19 (d, J = 8,7 Hz, 1 H), 7,49 (d, J = 1,9 Hz, 1 H), 7,83 (d, J = 8,8 Hz, 2 H).

(3) ácido 4-{[1-(5-cloro-1-metil-1H-indol-2-il)heptil]amino}benzoico

A una mezcla de 4-{[1-(5-cloro-1-metil-1H-indol-2-il)heptil]amino}benzoato de metilo (1,15 g) sintetizado con anterioridad, tetrahidrofurano (15 mL) y etanol (15 mL) se añadió solución acuosa 1 N de hidróxido de sodio (15 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en

1534

agua (30 mL) y ácido clorhídrico 1 N (15 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (1,09 g, 98%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 (t, J = 6,5 Hz, 3 H), 1,11 - 1,51 (m, 8 H), 1,79 - 2,04 (m, 2 H), 3,58 (s, 3 H), 4,49 - 4,63 (m, 1 H), 6,31 (s, 1 H), 6,42 (d, J = 8,3 Hz, 2 H), 7,05 - 7,17 (m, 2 H), 7,46 (s, 1 H), 7,80 (d, J = 8,3 Hz, 2 H).

(4) 3-{[(4-{[1-(5-cloro-1-metil-1H-indol-2-il)heptil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[1-(5-cloro-1-metil-1H-indol-2-il)heptil]amino}benzoico (300 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (174 mg), monohidrato de 1-hidroxibenzotriazol (173 mg), trietilamina (158 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (217 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (349 mg, 93%) en forma de un aceite amarillo pálido.

1535

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,88 (t, J = 6,9 Hz, 3 H), 1,18 - 1,55 (m, 11 H), 1,87 - 2,10 (m, 2 H), 2,60 (t, J = 5,8 Hz, 2 H), 3,61 - 3,76 (m, 5 H), 4,06 - 4,23 (m, 3 H), 4,57 - 4,69 (m, 1 H), 6,37 (s, 1 H), 6,57 (d, J = 8,5 Hz, 2 H), 6,64 (t, J = 5,8 Hz, 1 H), 7,11 - 7,16 (m, 1 H), 7,17 - 7,23 (m, 1 H), 7,50 (d, J = 1,6 Hz, 1 H), 7,59 (d, J = 8,5 Hz, 2 H).

(5) ácido 3-{[(4-{[1-(5-cloro-1-metil-1H-indol-2-il)heptil]amino}fenil)carbonil]amino}propanoico

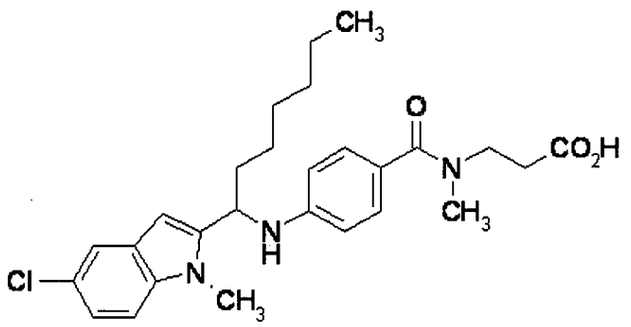
A una mezcla de 3-{[(4-{[1-(5-cloro-1-metil-1H-indol-2-il)heptil]amino}fenil)carbonil]amino}propanoato de etilo (349 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 3 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (302 mg, 92%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 (t, J = 6,4 Hz, 3 H), 1,17 - 1,55 (m, 8 H), 1,84 - 2,05 (m, 2 H), 2,62 (t, J = 5,7 Hz, 2 H), 3,58 - 3,72 (m, 5 H), 4,60 (t, J = 6,8 Hz, 1 H), 6,33 (s, 1 H), 6,52 (d, J = 8,7 Hz, 2 H), 6,69 (t, J = 5,8 Hz, 1 H), 7,12 (dd, J = 9,0, 2,1 Hz, 1 H), 7,17 (d, J = 9,0 Hz, 1 H), 7,47 (d, J = 2,1 Hz, 1 H), 7,55 (d, J = 8,7 Hz, 2 H).

Ejemplo A141

Ácido 3-{[(4-{[1-(5-cloro-1-metil-1H-indol-2-il)heptil]amino}fenil)carbonil](metil)amino}propanoico

1536



(1) 3-{[(4-{[1-(5-cloro-1-metil-1H-indol-2-il)heptil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[1-(5-cloro-1-metil-1H-indol-2-il)heptil]amino}benzoico (300 mg) sintetizado en el Ejemplo A140(3), 3-(metilamino)propanoato de etilo (148 mg), monohidrato de 1-hidroxibenzotriazol (173 mg), trietilamina (158 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (217 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (235 mg, 61%) en forma de un aceite amarillo pálido.

1537

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,87 (t, J = 6,6 Hz, 3 H), 1,17 - 1,53 (m, 11 H), 1,89 - 2,06 (m, 2 H), 2,63 (t, J = 6,7 Hz, 2 H), 3,04 (s, 3 H), 3,65 - 3,79 (m, 5 H), 4,02 (d, J = 7,1 Hz, 1 H), 4,12 (q, J = 7,1 Hz, 2 H), 4,54 - 4,65 (m, 1 H), 6,37 (s, 1 H), 6,55 (d, J = 8,4 Hz, 2 H), 7,13 (dd, J = 8,8, 1,8 Hz, 1 H), 7,20 (d, J = 8,8 Hz, 1 H), 7,25 (d, J = 8,4 Hz, 2 H), 7,50 (d, J = 1,8 Hz, 1 H).

(2) ácido 3-{[(4-{[1-(5-cloro-1-metil-1H-indol-2-il)heptil]amino}fenil)carbonil](metil)amino}propanoico

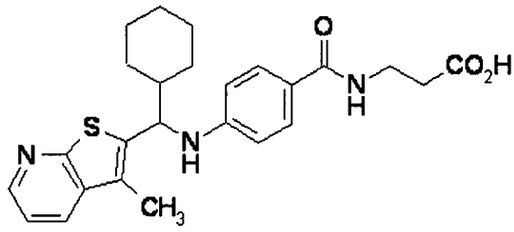
A una mezcla de 3-{[(4-{[1-(5-cloro-1-metil-1H-indol-2-il)heptil]amino}fenil)carbonil](metil)amino}propanoato de etilo (235 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (211 mg, 95%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,87 (t, J = 6,8 Hz, 3 H), 1,16 - 1,54 (m, 8 H), 1,84 - 2,05 (m, 2 H), 2,63 (t, J = 5,8 Hz, 2 H), 3,02 (s, 3 H), 3,62 - 3,76 (m, 5 H), 4,59 (t, J = 6,8 Hz, 1 H), 6,35 (s, 1 H), 6,53 (d, J = 8,5 Hz, 2 H), 7,12 (dd, J = 8,7, 1,9 Hz, 1 H), 7,19 (d, J = 8,7 Hz, 1 H), 7,24 (d, J = 8,5 Hz, 2 H), 7,49 (d, J = 1,9 Hz, 1 H).

Ejemplo A142

1538

Ácido 3-{[(4-{[ciclohexil(3-metiltieno[2,3-b]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoico




(1) 3-metiltieno[2,3-b]piridin-2-carboxilato de etilo

A una solución (300 mL) de 2-cloropiridin-3-carbonitrilo (15,0 g) en tetrahidrofurano se añadió una solución 3,0 M (72,5 mL) de cloruro de metilmagnesio en tetrahidrofurano a -78 °C y la mezcla se agitó a temperatura ambiente durante 10 h bajo una atmósfera de nitrógeno. A la mezcla de reacción se añadió agua (50 mL) y luego se añadió ácido sulfúrico al 10% (100 mL) y la mezcla se agitó durante la noche. Se agregó carbonato de sodio para acidificar la mezcla de reacción hasta pH = 9 y la mezcla se extrajo con acetato de etilo. El extracto se secó con sulfato de sodio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice para dar un aceite incoloro (7,68 g). A una mezcla del aceite obtenido (7,00 g), mercaptoacetato de etilo (13 mL) y N,N-dimetilformamida anhidra (200 mL) se añadió hidruro de sodio (60%, oleoso, 4,68 g) a 5 °C durante 30 min y la mezcla se agitó a 5 °C durante 20 min, luego a temperatura ambiente durante 18 h. Se añadió solución saturada acuosa de carbonato ácido de sodio

1539

para neutralizar la reacción y la mezcla se vertió en agua. El sólido precipitado se recogió por filtración y se recristalizó en éter de petróleo/acetato de etilo para dar el compuesto objeto del título (6,14 g, 29%) en forma de un sólido blanco.

$^1$H RMN (400 MHz, $CDCl_3$) δ ppm 1,45 (t, J = 7,2 Hz, 3H), 2,78 (s, 3H), 4,43 (q, J = 7,2 Hz, 2H), 7,38-7,40 (m, 1H), 8,11-8,13 (m, 1H), 8,70-8,72 (m, 1H).

(2) 3-metiltieno[2,3-b]piridin-2-carbaldehído

A una mezcla de 3-metiltieno[2,3-b]piridin-2-carboxilato de etilo (3,00 g) sintetizado con anterioridad, cloruro de calcio (3,02 g), etanol (50 mL) y tetrahidrofurano (50 mL) se añadió borohidruro de sodio (2,06 g) a 0 °C y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido blanco. A una solución (50 mL) del sólido obtenido en tetrahidrofurano se añadió dióxido de manganeso activo (12,5 g) y la mezcla se agitó a 50 °C durante la noche. El dióxido de manganeso se filtró y el filtrado se concentró a presión reducida. El residuo se lavó con éter diisopropílico para dar el compuesto objeto del título (2,07 g, 86%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,79 (s, 3 H), 7,39 (dd, J = 8,2, 4,5 Hz, 1 H), 8,16 (dd, J = 8,2, 1,6 Hz, 1 H), 8,72 (dd, J = 4,5, 1,6 Hz, 1 H), 10,36 (s, 1 H).

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(3) ciclohexil(3-metiltieno[2,3-b]piridin-2-il)metanona

A una solución (60 mL) de 3-metiltieno[2,3-b]piridin-2-carbaldehído (2,07 g) sintetizado con anterioridad en tetrahidrofurano se añadió una solución 1,0 M (17,6 mL) de bromuro de ciclohexilmagnesio en tetrahidrofurano a 0 °C y la mezcla se agitó durante 1 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (10 - 50% de acetato de etilo/hexano) para dar un sólido amarillo. A una mezcla del sólido obtenido, N-óxido de 4-metilmorfolina (1,81 g) y acetonitrilo (40 mL) se añadió perrutenato de tetrapropilamonio (238 mg) y la mezcla se agitó a temperatura ambiente durante 3 h y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 30% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,50 g, 85%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,18 - 1,62 (m, 5 H), 1,69 - 1,80 (m, 1 H), 1,81 - 1,91 (m, 2 H), 1,95 - 2,06 (m, 2 H), 2,73 (s, 3 H), 2,95 - 3,07 (m, 1 H), 7,37 (m, J = 8,2, 4,4 Hz, 1 H), 8,13 (dd, J = 8,2, 1,6 Hz, 1 H), 8,70 (dd, J = 4,4, 1,6 Hz, 1 H).

(4) 4-{[ciclohexil(3-metilfuro[2,3-b]piridin-2-il)metil]amino}benzoato de metilo

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A una mezcla de ciclohexil(3-metiltieno[2,3-b]piridin-2-il)metanona (1,00 g) sintetizada con anterioridad, 4-aminobenzoato de metilo (642 mg), trietilamina (4,31 mL) y cloruro de metileno (20 mL) se añadió cloruro de titanio (IV) (508 µL) a 0 °C y la mezcla se agitó a temperatura ambiente durante 1,5 días bajo una atmósfera de argón. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido marrón oscuro. A una solución (20 mL) del sólido obtenido en tetrahidrofurano se añadieron ácido acético (442 µL) y cianoborohidruro de sodio (485 mg) y la mezcla se agitó a temperatura ambiente durante 1,5 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (975 mg, 64%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 1,35 (m, 5 H), 1,48 - 1,96 (m, 5 H), 2,02 - 2,19 (m, 1 H), 2,55 (s, 3 H), 3,81 (s, 3 H), 4,54 - 4,70 (m, 2 H), 6,51 (d, J = 8,8 Hz, 2 H), 7,59 (dd, J = 7,6, 5,7 Hz, 1 H), 7,78 (d, J = 8,8 Hz, 2 H), 8,22 (d, J = 7,6 Hz, 1 H), 8,63 (d, J = 5,7 Hz, 1 H).

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(5) ácido 4-{[ciclohexil(3-metilfuro[2,3-b]piridin-2-il)metil]amino}benzoico

A una mezcla de 4-{[ciclohexil(3-metilfuro[2,3-b]piridin-2-il)metil]amino}benzoato de metilo (975 mg) sintetizado con anterioridad, tetrahidrofurano (10 mL) y etanol (10 mL) se añadió solución acuosa 1 N de hidróxido de sodio (10 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (20 mL), se añadió ácido clorhídrico 1 N (10 mL) y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (701 mg, 75%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,01 - 1,39 (m, 5 H), 1,53 - 1,92 (m, 5 H), 2,07 - 2,20 (m, 1 H), 2,46 (s, 3 H), 4,60 (d, J = 8,0 Hz, 1 H), 6,53 (d, J = 8,5 Hz, 2 H), 7,21 - 7,31 (m, 1 H), 7,82 (d, J = 8,5 Hz, 2 H), 7,87 (dd, J = 8,1, 1,3 Hz, 1 H), 8,47 (dd, J = 4,4, 1,3 Hz, 1 H).

(6) 3-{[(4-{[ciclohexil(3-metiltieno[2,3-b]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclohexil(3-metilfuro[2,3-b]piridin-2-il)metil]amino}benzoico (300 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (181 mg), monohidrato de 1-hidroxibenzotriazol (181 mg), trietilamina (329 µL) y N,N-dimetilformamida (10 mL) se

(53B

añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (226 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 100% de acetato de etilo/hexano) para dar el compuesto objeto del título (335 mg, 89%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,38 (m, 8 H), 1,54 - 1,90 (m, 5 H), 2,08 - 2,21 (m, 1 H), 2,45 (s, 3 H), 2,56 (t, J = 5,9 Hz, 2 H), 3,59 - 3,69 (m, 2 H), 4,12 (q, J = 7,1 Hz, 2 H), 4,40 (d, J = 6,3 Hz, 1 H), 4,53 - 4,61 (m, 1 H), 6,48 - 6,64 (m, 3 H), 7,21 - 7,30 (m, 1 H), 7,52 (d, J = 8,5 Hz, 2 H), 7,86 (dd, J = 8,1, 1,5 Hz, 1 H), 8,45 (dd, J = 4,5, 1,5 Hz, 1 H).

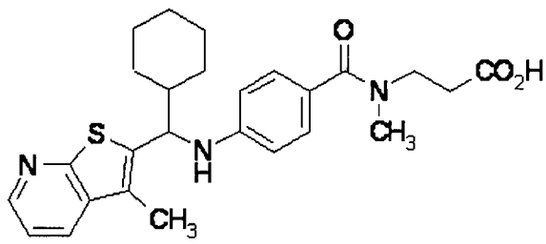
(7) ácido 3-{[(4-{[ciclohexil(3-metiltieno[2,3-b]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoico

A una mezcla de 3-{[(4-{[ciclohexil(3-metiltieno[2,3-b]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo (335 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido

clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (281 mg, 89%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 1,34 (m, 5 H), 1,51 - 1,87 (m, 5 H), 2,06 - 2,19 (m, 1 H), 2,44 (s, 3 H), 2,52 - 2,64 (m, 2 H), 3,53 - 3,68 (m, 2 H), 4,55 (d, J = 8,0 Hz, 1 H), 6,49 (d, J = 8,7 Hz, 2 H), 6,71 (t, J = 5,3 Hz, 1 H), 7,23 - 7,31 (m, 1 H), 7,49 (d, J = 8,7 Hz, 2 H), 7,88 (dd, J = 8,0, 1,1 Hz, 1 H), 8,45 (dd, J = 4,5, 1,1 Hz, 1 H).

Ejemplo A143

Ácido 3-{[(4-{[ciclohexil(3-metiltieno[2,3-b]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) 3-{[(4-{[ciclohexil(3-metiltieno[2,3-b]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclohexil(3-metilfuro[2,3-b]piridin-2-il)metil]amino}benzoico (300 mg) sintetizado en el Ejemplo A142(5), 3-(metilamino)propanoato de etilo (155 mg), monohidrato de 1-hidroxibenzotriazol (181 mg), trietilamina (329 µL) y N,N-dimetilformamida (10 mL) se

1545

añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (226 mg) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (40 - 100% de acetato de etilo/hexano) para dar el compuesto objeto del título (333 mg, 85%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 1,37 (m, 8 H), 1,52 - 1,89 (m, 5 H), 2,07 - 2,21 (m, 1 H), 2,45 (s, 3 H), 2,60 (t, J = 6,8 Hz, 2 H), 2,99 (s, 3 H), 3,69 (t, J = 6,8 Hz, 2 H), 4,02 - 4,17 (m, 2 H), 4,32 (d, J = 5,8 Hz, 1 H), 4,49 - 4,58 (m, 1 H), 6,52 (d, J = 8,5 Hz, 2 H), 7,19 (d, J = 8,5 Hz, 2 H), 7,22 - 7,31 (m, 1 H), 7,86 (dd, J = 8,0, 1,1 Hz, 1 H), 8,43 - 8,50 (m, 1 H).

(2) ácido 3-{[(4-{[ciclohexil(3-metiltieno[2,3-b]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

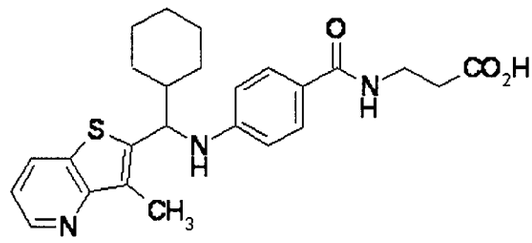
A una mezcla de 3-{[(4-{[ciclohexil(3-metiltieno[2,3-b]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (333 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 4 h y se concentró a presión

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reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (275 mg, 88%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,02 - 1,35 (m, 5 H), 1,54 - 1,88 (m, 5 H), 2,07 - 2,19 (m, 1 H), 2,45 (s, 3 H), 2,58 - 2,70 (m, 2 H), 3,01 (s, 3 H), 3,68 (t, J = 6,6 Hz, 2 H), 4,54 (d, J = 7,6 Hz, 1 H), 6,51 (d, J = 8,7 Hz, 2 H), 7,20 (d, J = 8,7 Hz, 2 H), 7,27 (dd, J = 8,1, 4,7 Hz, 1 H), 7,88 (dd, J = 8,1, 1,6 Hz, 1 H), 8,47 (dd, J = 4,7, 1,6 Hz, 1 H).

Ejemplo A144

Ácido 3-{[(4-{[ciclohexil(3-metiltieno[3,2-b]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoico




(1) 3-metiltieno[3,2-b]piridin-2-carboxilato de etilo

A una solución (100 mL) de 3-cloropiridin-2-carbonitrilo (10,0 g) en tetrahidrofurano se añadió una solución 3,0 M (48,0 mL) de bromuro de metilmagnesio en éter dietílico y la mezcla se agitó a temperatura ambiente durante 3 h. A la mezcla de reacción se añadió ácido clorhídrico 2 N (300 mL), tetrahidrofurano se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con

1547

salmuera saturada, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar un aceite de color amarillo pálido. A una mezcla del aceite obtenido, mercaptoacetato de etilo (4,23 mL) y N,N-dimetilformamida (60 mL) se añadió y carbonato de potasio (16,0 g) y la mezcla se agitó durante la noche a 50 °C. Se añadió agua para neutralizar la reacción y el sólido precipitado se recogió por filtración para dar el compuesto objeto del título (6,75 g, 79%) en forma de un sólido blanco.

$^1$H RMN (400 MHz, $CDCl_3$) δ ppm 1,44 (t, J = 7,2 Hz, 3 H), 2,87 (s, 3 H), 4,44 (q, J = 7,2 Hz, 2 H), 7,37 (dd, J = 8,3, 4,4 Hz, 1 H), 8,17 (dd, J = 8,3, 1,5 Hz, 1 H), 8,78 (dd, J = 4,4, 1,5 Hz, 1 H).

(2) 3-metiltieno[3,2-b]piridin-2-carbaldehído

A una mezcla de 3-metiltieno[3,2-b]piridin-2-carboxilato de etilo (3,00 g) sintetizado con anterioridad, cloruro de calcio (3,02 g), etanol (30 mL) y tetrahidrofurano (30 mL) se añadió borohidruro de sodio (2,06 g) a 0 °C y la mezcla se agitó a temperatura ambiente durante 5 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido blanco. A una solución (50 mL) del sólido obtenido en tetrahidrofurano se añadió dióxido de manganeso activo (12,2 g) y la mezcla se agitó a 50 °C durante la

1548

noche. El dióxido de manganeso se filtró y el filtrado se concentró a presión reducida para dar el compuesto objeto del título (2,24 g, 93%) en forma de un sólido blanco.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,90 (s, 3 H), 7,40 (dd, J = 8,2, 4,6 Hz, 1 H), 8,21 (dd, J = 8,2, 1,4 Hz, 1 H), 8,79 (dd, J = 4,6, 1,4 Hz, 1 H), 10,43 (s, 1 H).

(3) ciclohexil(3-metiltieno[3,2-b]piridin-2-il)metanona

A una solución (50 mL) de 3-metiltieno[3,2-b]piridin-2-carbaldehído (2,24 g) sintetizado con anterioridad en tetrahidrofurano se añadió una solución 1,0 M (18,9 mL) de bromuro de ciclohexilmagnesio en tetrahidrofurano a 0 °C y la mezcla se agitó a 0 °C durante 1,5 h bajo una atmósfera de argón. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (10 - 50% de acetato de etilo/hexano) para dar un aceite de color amarillo pálido. A una mezcla del aceite obtenido, N-óxido de 4-metilmorfolina (1,81 g) y acetonitrilo (40 mL) se añadió perrutenato de tetrapropilamonio (238 mg) y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 30% de acetato de etilo/hexano) para dar el compuesto objeto del título (1,38 g, 79%) en forma de un aceite incoloro.

1549

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,19 - 1,65 (m, 5 H), 1,70 - 1,81 (m, 1 H), 1,82 - 1,94 (m, 2 H), 1,94 - 2,08 (m, 2 H), 2,86 (s, 3 H), 3,01 - 3,15 (m, 1 H), 7,37 (dd, J = 8,2, 4,4 Hz, 1 H), 8,17 (dd, J = 8,2, 1,5 Hz, 1 H), 8,78 (dd, J = 4,4, 1,5 Hz, 1 H).

(4) 4-{[ciclohexil(3-metiltieno[3,2-b]piridin-2-il)metil]amino}benzoato de metilo

A una mezcla de ciclohexil(3-metiltieno[3,2-b]piridin-2-il)metanona (1,38 g) sintetizada con anterioridad, 4-aminobenzoato de metilo (884 mg), trietilamina (5,94 mL) y cloruro de metileno (30 mL) se añadió cloruro de titanio (IV) (700 µL) a 0 °C y la mezcla se agitó a temperatura ambiente durante 3,5 días bajo una atmósfera de argón. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (30 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (607 µL) y cianoborohidruro de sodio (666 mg) y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (10 - 50% de

1550

acetato de etilo/hexano) para dar el compuesto objeto del título (1,31 g, 62%) en forma de un sólido marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,07 - 1,37 (m, 5 H), 1,55 - 1,90 (m, 5 H), 2,03 - 2,16 (m, 1 H), 2,59 (s, 3 H), 3,79 (s, 3 H), 4,56 (d, J = 5,8 Hz, 1 H), 4,63 - 4,72 (m, 1 H), 6,51 (d, J = 8,5 Hz, 2 H), 7,16 (dd, J = 8,1, 4,6 Hz, 1 H), 7,77 (d, J = 8,5 Hz, 2 H), 7,98 (dd, J = 8,1, 1,2 Hz, 1 H), 8,64 (dd, J = 4,6, 1,2 Hz, 1 H).

(5) ácido 4-{[ciclohexil(3-metiltieno[3,2-b]piridin-2-il)metil]amino}benzoico

A una mezcla de 4-{[ciclohexil(3-metiltieno[3,2-b]piridin-2-il)metil]amino}benzoato de metilo (1,31 g) sintetizado con anterioridad, tetrahidrofurano (10 mL) y etanol (10 mL) se añadió solución acuosa 1 N de hidróxido de sodio (10 mL) y la mezcla se agitó durante la noche con calentamiento a reflujo. Se añadió además solución acuosa 1 N de hidróxido de sodio (5 mL) y la mezcla luego se agitó con calentamiento a reflujo durante 7 h y se concentró a presión reducida. El residuo se disolvió en agua (20 mL) y ácido clorhídrico 1 N (15 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración y el sólido marrón obtenido se disolvió en acetato de etilo. La solución se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con éter diisopropílico para dar el compuesto objeto del título (804 mg, 64%) en forma de un sólido marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,07 - 1,36 (m, 5 H), 1,55 - 1,91 (m, 5 H), 2,02 - 2,15 (m, 1 H), 2,60 (s, 3 H), 4,52 -

4,74 (m, 2 H), 6,52 (d, J = 8,7 Hz, 2 H), 7,17 (dd, J = 8,0, 4,6 Hz, 1 H), 7,82 (d, J = 8,7 Hz, 2 H), 7,99 (dd, J = 8,0, 1,4 Hz, 1 H), 8,66 (dd, J = 4,6, 1,4 Hz, 1 H).

(6) 3-{[(4-{[ciclohexil(3-metiltieno[3,2-b]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclohexil(3-metiltieno[3,2-b]piridin-2-il)metil]amino}benzoico (300 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (181 mg), monohidrato de 1-hidroxibenzotriazol (181 mg), trietilamina (329 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (226 mg) y la mezcla se agitó a temperatura ambiente durante 1 día. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (60 - 100% de acetato de etilo/hexano) para dar el compuesto objeto del título (330 mg, 87%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,07 - 1,36 (m, 8 H), 1,56 - 1,90 (m, 5 H), 2,02 - 2,16 (m, 1 H), 2,52 - 2,63 (m, 5 H), 3,59 - 3,68 (m, 2 H), 4,12 (q, J = 7,1 Hz, 2 H), 4,49 (d, J = 5,8 Hz, 1 H), 4,62 - 4,69 (m, 1 H), 6,52 (d, J = 8,5 Hz, 2 H), 6,59 (t, J = 5,8 Hz, 1 H), 7,16 (dd, J = 8,1, 4,6 Hz, 1

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H), 7,52 (d, J = 8,5 Hz, 2 H), 7,99 (dd, J = 8,1, 1,4 Hz, 1 H), 8,64 (dd, J = 4,6, 1,4 Hz, 1 H).

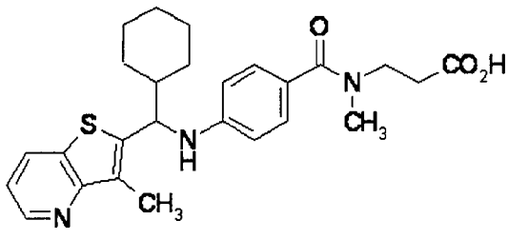
(7) ácido 3-{[(4-{[ciclohexil(3-metiltieno[3,2-b]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoico

A una mezcla de 3-{[(4-{[ciclohexil(3-metiltieno[3,2-b]piridin-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo (330 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (291 mg, 94%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,07 - 1,36 (m, 5 H), 1,55 - 1,89 (m, 5 H), 2,03 - 2,14 (m, 1 H), 2,57 (s, 3 H), 2,63 (t, J = 5,7 Hz, 2 H), 3,55 - 3,77 (m, 2 H), 4,64 (d, J = 7,2 Hz, 1 H), 6,49 (d, J = 8,9 Hz, 2 H), 6,78 (t, J = 6,0 Hz, 1 H), 7,19 (dd, J = 8,0, 4,6 Hz, 1 H), 7,53 (d, J = 8,9 Hz, 2 H), 8,01 (dd, J = 8,0, 1,5 Hz, 1 H), 8,64 (dd, J = 4,6, 1,5 Hz, 1 H).

Ejemplo A145

Ácido 3-{[(4-{[ciclohexil(3-metiltieno[3,2-b]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

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(1) 3-{[(4-{[ciclohexil(3-metiltieno[3,2-b]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de ácido 4-{[ciclohexil(3-metiltieno[3,2-b]piridin-2-il)metil]amino}benzoico (300 mg) sintetizado en el Ejemplo A144(5), 3-(metilamino)propanoato de etilo (155 mg), monohidrato de 1-hidroxibenzotriazol (181 mg), trietilamina (329 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (226 mg) y la mezcla se agitó a temperatura ambiente durante 1 día. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (50 - 100% de acetato de etilo/hexano) para dar el compuesto objeto del título (325 mg, 84%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,07 - 1,36 (m, 8 H), 1,54 - 1,92 (m, 5 H), 2,01 - 2,16 (m, 1 H), 2,51 - 2,68 (m, 5 H),

1554

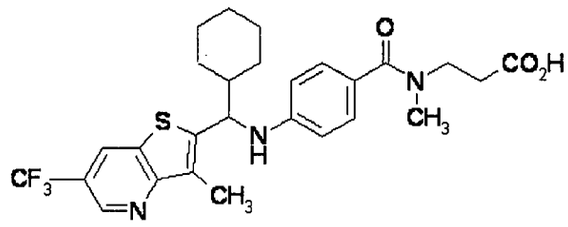
2,99 (s, 3 H), 3,69 (t, J = 7,0 Hz, 2 H), 4,10 (q, J = 6,9 Hz, 2 H), 4,36 (d, J = 5,2 Hz, 1 H), 4,58 - 4,67 (m, 1 H), 6,51 (d, J = 8,5 Hz, 2 H), 7,13 - 7,23 (m, 3 H), 8,00 (d, J = 8,0 Hz, 1 H), 8,64 (d, J = 4,4 Hz, 1 H).

(2) ácido 3-{[(4-{[ciclohexil(3-metiltieno[3,2-b]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

A una mezcla de 3-{[(4-{[ciclohexil(3-metiltieno[3,2-b]piridin-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (325 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (277 mg, 90%) en forma de un sólido blanco. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,06 - 1,34 (m, 5 H), 1,55 - 1,88 (m, 5 H), 2,03 - 2,15 (m, 1 H), 2,58 (s, 3 H), 2,66 (t, J = 6,3 Hz, 2 H), 3,02 (s, 3 H), 3,70 (t, J = 6,3 Hz, 2 H), 4,62 (d, J = 7,5 Hz, 1 H), 6,50 (d, J = 8,7 Hz, 2 H), 7,15 - 7,25 (m, 3 H), 8,01 (dd, J = 8,3, 1,5 Hz, 1 H), 8,66 (dd, J = 4,5, 1,5 Hz, 1 H).

Ejemplo A146

Ácido 3-[{[4-({ciclohexil[3-metil-6-(trifluorometil)tieno[3,2-b]piridin-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



(1) 3-metil-6-(trifluorometil)tieno[3,2-b]piridin-2-carboxilato de etilo

A una solución (50 mL) de 3-cloro-5-(trifluorometil)piridin-2-carbonitrilo (5,00 g) en tetrahidrofurano se añadió una solución 3,0 M (16,1 mL) de bromuro de metilmagnesio en éter dietílico a 0 °C y la mezcla se agitó durante 3 h bajo una atmósfera de argón. A la mezcla de reacción se añadió ácido clorhídrico 1 N (300 mL) para acidificar la solución a pH = 3 - 4 y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 10% de acetato de etilo/hexano) para dar un sólido de color amarillo pálido. A una mezcla del sólido obtenido, mercaptoacetato de etilo (1,61 mL) y N,N-dimetilformamida (30 mL) se añadió carbonato de potasio (5,56 g) y la mezcla se agitó a 50 °C durante 10 h. Se añadió agua para neutralizar la reacción y el sólido precipitado se recogió por filtración para dar el compuesto objeto del título (3,76 g, 54%) en forma de un sólido blanco.

1556

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,45 (t, J = 7,1 Hz, 3 H), 2,88 (s, 3 H), 4,45 (q, J = 7,1 Hz, 2 H), 8,39 - 8,45 (m, 1 H), 8,94 - 9,02 (m, 1 H).

(2) 3-metil-6-(trifluorometil)tieno[3,2-b]piridin-2-carbaldehído

A una mezcla de 3-metil-6-(trifluorometil)tieno[3,2-b]piridin-2-carboxilato de etilo (3,69 g) sintetizado con anterioridad, cloruro de calcio (2,84 g), etanol (40 mL) y tetrahidrofurano (40 mL) se añadió borohidruro de sodio (1,94 g) a 0 °C y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido blanco. A una solución (60 mL) del sólido obtenido en tetrahidrofurano se añadió dióxido de manganeso activo (16,3 g) y la mezcla se agitó a 50 °C durante 5 h. El dióxido de manganeso se filtró y el filtrado se concentró a presión reducida para dar el compuesto objeto del título (2,88 g, 92%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,93 (s, 3 H), 8,47 - 8,50 (m, 1 H), 9,00 (d, J = 1,6 Hz, 1 H), 10,46 (s, 1 H).

(3) ciclohexil[3-metil-6-(trifluorometil)tieno[3,2-b]piridin-2-il]metanona

A una solución (15 mL) de 3-metil-6-(trifluorometil)tieno[3,2-b]piridin-2-carbaldehído (1,44 g) sintetizado con anterioridad en tetrahidrofurano se añadió

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solución 1,0 M (8,81 mL) de bromuro de ciclohexilmagnesio en tetrahidrofurano a 0 °C y la mezcla se agitó durante 1 h bajo una atmósfera de argón. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (10 - 50% de acetato de etilo/hexano) para dar un aceite amarillo. A una mezcla del aceite obtenido, N-óxido de 4-metilmorfolina (817 mg) y acetonitrilo (20 mL) se añadió perrutenato de tetrapropilamonio (108 mg) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 10% de acetato de etilo/hexano) para dar el compuesto objeto del título (805 mg, 42%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,19 - 1,65 (m, 5 H), 1,70 - 1,81 (m, 1 H), 1,82 - 2,07 (m, 4 H), 2,86 (s, 3 H), 3,01 - 3,15 (m, 1 H), 8,42 (s, 1 H), 8,98 (s, 1 H).

(4) 4-({ciclohexil[3-metil-6-(trifluorometil)tieno[3,2-b]piridin-2-il]metil}amino)benzoato de metilo

A una mezcla de ciclohexil[3-metil-6-(trifluorometil)tieno[3,2-b]piridin-2-il]metanona (805 mg) sintetizada con anterioridad, 4-aminobenzoato de metilo (410 mg), trietilamina (2,75 mL) y cloruro de metileno (10 mL) se añadió cloruro de titanio (IV) (323 µL) a 0 °C y la mezcla se agitó a temperatura ambiente durante 1 día bajo una atmósfera

1558

de argón. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite de color marrón oscuro. A una solución (10 mL) del aceite obtenido en tetrahidrofurano se añadieron ácido acético (282 µL) y cianoborohidruro de sodio (309 mg) y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadió solución saturada acuosa de hidrógeno-carbonato de sodio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 40% de acetato de etilo/hexano) para dar el compuesto objeto del título (775 mg, 68%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,05 - 1,36 (m, 5 H), 1,53 - 1,91 (m, 5 H), 2,02 - 2,15 (m, 1 H), 2,62 (s, 3 H), 3,79 (s, 3 H), 4,58 (d, J = 5,5 Hz, 1 H), 4,66 - 4,74 (m, 1 H), 6,50 (d, J = 8,8 Hz, 2 H), 7,77 (d, J = 8,8 Hz, 2 H), 8,23 (d, J = 1,3 Hz, 1 H), 8,87 (d, J = 1,3 Hz, 1 H).

(5) ácido 4-({ciclohexil[3-metil-6-(trifluorometil)tieno[3,2-b]piridin-2-il]metil}amino)benzoico

A una mezcla de 4-({ciclohexil[3-metil-6-(trifluorometil)tieno[3,2-b]piridin-2-il]metil}amino)benzoato de metilo (775 mg) sintetizado con anterioridad, tetrahidrofurano (10 mL) y etanol (10 mL) se añadió solución

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acuosa 1 N de hidróxido de sodio (10 mL) y la mezcla se agitó durante 1 día con calentamiento a reflujo y se concentró a presión reducida. El residuo se disolvió en agua (20 mL) y ácido clorhídrico 1 N (10 mL) se añadió a 0 °C y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (671 mg, 87%) en forma de un sólido de color marrón pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,07 - 1,38 (m, 5 H), 1,53 - 1,93 (m, 5 H), 2,00 - 2,14 (m, 1 H), 2,62 (s, 3 H), 4,55 - 4,80 (m, 2 H), 6,50 (d, J = 8,8 Hz, 2 H), 7,82 (d, J = 8,8 Hz, 2 H), 8,23 (d, J = 1,3 Hz, 1 H), 8,88 (d, J = 1,3 Hz, 1 H).

(6) 3-[{[4-({ciclohexil[3-metil-6-(trifluorometil)tieno[3,2-b]piridin-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

A una mezcla de ácido 4-({ciclohexil[3-metil-6-(trifluorometil)tieno[3,2-b]piridin-2-il]metil}amino)benzoico (343 mg) sintetizado con anterioridad, 3-(metilamino)propanoato de etilo (151 mg), monohidrato de 1-hidroxibenzotriazol (176 mg), trietilamina (321 µL) y N,N-dimetilformamida (10 mL) se añadió clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (221 mg) y la mezcla se agitó a temperatura ambiente durante 2,5 días. Se añadió

1560

solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de acetato de etilo/hexano) para dar el compuesto objeto del título (310 mg, 72%) en forma de un sólido blanco.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,08 - 1,35 (m, 8 H), 1,54 - 1,92 (m, 5 H), 2,01 - 2,13 (m, 1 H), 2,51 - 2,68 (m, 5 H), 2,99 (s, 3 H), 3,69 (t, J = 7,0 Hz, 2 H), 4,10 (q, J = 7,1 Hz, 2 H), 4,37 - 4,46 (m, 1 H), 4,60 - 4,68 (m, 1 H), 6,49 (d, J = 8,7 Hz, 2 H), 7,19 (d, J = 8,7 Hz, 2 H), 8,24 (s, 1 H), 8,87 (s, 1 H).

(7) ácido 3-[{[4-({ciclohexil[3-metil-6-(trifluorometil)tieno[3,2-b]piridin-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

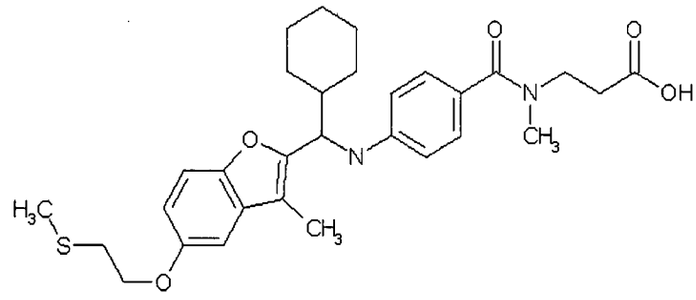
A una mezcla de 3-[{[4-({ciclohexil[3-metil-6-(trifluorometil)tieno[3,2-b]piridin-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (310 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL), ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (284 mg, 96%) en forma de un sólido blanco.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,07 - 1,35 (m, 5 H), 1,53 - 1,89 (m, 5 H), 2,00 - 2,12 (m, 1 H), 2,54 - 2,69 (m, 5 H), 3,00 (s, 3 H), 3,68 (t, J = 6,6 Hz, 2 H), 4,64 (d, J = 7,2 Hz, 1 H), 6,49 (d, J = 8,3 Hz, 2 H), 7,20 (d, J = 8,3 Hz, 2 H), 8,25 (s, 1 H), 8,88 (s, 1 H).

Ejemplo A147

Ácido 3-[({4-[(ciclohexil{3-metil-5-[2-(metiltio)etoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico




(1) ciclohexil{3-metil-5-[2-(metilsulfanil)etoxi]-1-benzofuran-2-il}metanona

Ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metanona (0,76 g) sintetizada en el Ejemplo A82(3) se disolvió en tetrahidrofurano (15 mL) y 2-(metiltio)etanol (0,26 mL), tributilfosfina (1,5 mL) y 1,1'-(azodicarbonil)dipiperidina (1,46 g) se añadieron a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 12 h. Hexano (15 mL) se añadió a la mezcla y el precipitado se filtró a través de celite. Se añadió agua al filtrado y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida

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y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (0,73 g, 76%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,18 - 2,01 (m, 10 H), 2,24 (s, 3 H), 2,57 (s, 3 H), 2,92 (t, J = 6,8 Hz, 2 H), 3,25 - 3,40 (m, 1 H), 4,21 (t, J = 6,8 Hz, 2 H), 7,03 - 7,41 (m, 3 H).

(2) ciclohexil{3-metil-5-[2-(metilsulfanil)etoxi]-1-benzofuran-2-il}metanol

Ciclohexil{3-metil-5-[2-(metilsulfanil)etoxi]-1-benzofuran-2-il}metanona (0,73 g) sintetizada en el punto (1) antes mencionado se disolvió en a tetrahidrofurano (10 mL) y metanol (5 mL) y borohidruro de sodio (90%, 0,18 g) se añadió a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla se enfrió con hielo nuevamente, agua (1 mL) y ácido clorhídrico 1 N (5 mL) se añadieron cuidadosamente y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (0,67 g, 91%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 - 1,99 (m, 11 H), 2,19 (s, 3 H), 2,23 (s, 3 H), 2,91 (t, J = 6,9 Hz, 2 H), 4,20 (t, J = 6,9 Hz, 2 H), 4,51 (dd, J = 8,5, 6,0 Hz, 1 H), 6,79 - 6,98 (m, 2 H), 7,31 (d, J = 9,0 Hz, 1 H).

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(3) 3-[({4-[(ciclohexil{3-metil-5-[2-(metilsulfanil)etoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo

Ciclohexil{3-metil-5-[2-(metilsulfanil)etoxi]-1-benzofuran-2-il}metanol (0,34 g) sintetizado en el punto (2) antes mencionado se disolvió en tetrahidrofurano (5 mL) y cloruro de tionilo (0,13 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de hidrógeno-carbonato de sodio (10 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilacetamida (5 mL), yoduro de sodio (0,23 g), carbonato de sodio (0,15 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,25 g) sintetizado en el Ejemplo 2(2) se añadieron a la solución y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (0,33 g, 59%) en forma de un aceite amarillo.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 2,00 (m, 15 H), 2,05 (s, 3 H), 2,22 (s, 3 H), 2,61 (t, J = 6,8 Hz, 2 H), 2,89 (t, J = 6,9 Hz, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 6,8 Hz, 2 H), 4,00 - 4,20 (m, 4 H), 4,36 (d, J = 8,0 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,78 - 6,94 (m, 2 H), 7,14 - 7,25 (m, 3 H).

(4) ácido 3-[({4-[(ciclohexil{3-metil-5-[2-(metiltio)etoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

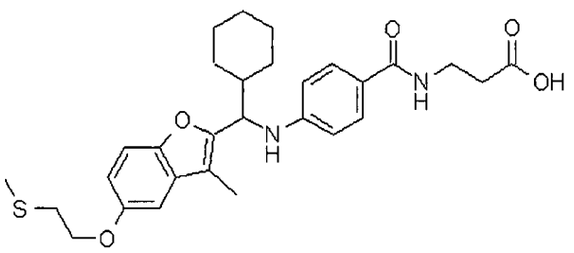
El 3-[({4-[(ciclohexil{3-metil-5-[2-(metilsulfanil)etoxi]-1-benzofuran-2-il}metiletilo amino]fenil}carbonil)(metil)amino]propanoato de (0,33 g) sintetizado en el punto (3) antes mencionado se disolvió en etanol (2 mL), una solución acuosa 1 N de hidróxido de sodio (1,5 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a 50 °C durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (1,5 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (0,20 g, 63%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,88 - 2,11 (m, 12 H), 2,15 (s, 3 H), 2,23 (s, 3 H), 2,40 - 2,46 (m, 2 H), 2,76 - 2,96 (m, 5 H), 3,50 (t, J = 7,3 Hz, 2 H), 4,15 (t, J = 6,7 Hz, 2 H), 4,37 (t, J = 8,3 Hz, 1 H), 6,46 (d, J = 8,1 Hz, 1 H), 6,59 (d, J = 8,7 Hz, 2 H), 6,80 (dd, J = 8,7, 2,6 Hz, 1 H), 7,03 (d, J = 2,6 Hz, 1 H), 7,09 (d, J = 8,7 Hz, 2 H), 7,32 (d, J = 8,7 Hz, 1 H).

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Ejemplo A148

Ácido 3-[({4-[(ciclohexil{3-metil-5-[2-(metiltio)etoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoico



Ciclohexil{3-metil-5-[2-(metilsulfanil)etoxi]-1-benzofuran-2-il}metanol sintetizado en el Ejemplo A147(2) se disolvió en tetrahidrofurano (5 mL) y cloruro de tionilo (0,13 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (10 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilacetamida (5 mL), se añadieron yoduro de sodio (0,23 g), carbonato de sodio (0,15 g) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,25 g) sintetizado en el Ejemplo 1(2) y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se

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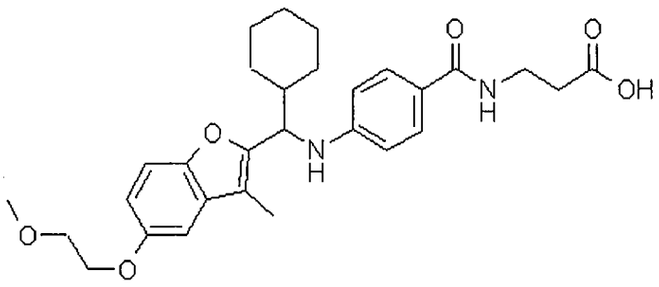
purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (0,38 g, 69%) en forma de un aceite amarillo. Esto se disolvió en etanol (2 mL), una solución acuosa 1 N de hidróxido de sodio (1,5 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a 50 °C durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (1,5 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (0,18 g, 49%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 0,88 - 2,10 (m, 12 H), 2,15 (s, 3 H), 2,23 (s, 3 H), 2,42 (t, J = 7,2 Hz, 2 H), 2,84 (t, J = 6,5 Hz, 2 H), 3,47 - 3,55 (m, 2 H), 4,15 (t, J = 6,6 Hz, 2 H), 4,41 (t, J = 8,4 Hz, 1 H), 6,49 - 6,64 (m, 3 H), 6,79 (dd, J = 8,9, 2,5 Hz, 1 H), 7,03 (d, J = 2,4 Hz, 1 H), 7,32 (d, J = 8,9 Hz, 1 H), 7,51 (d, J = 8,7 Hz, 2 H), 7,99 (t, J = 5,5 Hz, 1 H).

Ejemplo A149

Ácido 3-[{[4-({ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}amino]propanoico

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A una solución (15 mL) de ciclohexil[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]metanol (0,86 g) sintetizado en el Ejemplo A79(3) en tetrahidrofurano se añadió cloruro de tionilo (0,35 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y solución saturada acuosa de carbonato ácido de sodio (20 mL) se añadió cuidadosamente. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilacetamida (15 mL), yoduro de sodio (0,61 g), carbonato de sodio (0,41 g) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,64 g) sintetizado en el Ejemplo 1(2) se añadieron a la solución y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[5-(2-

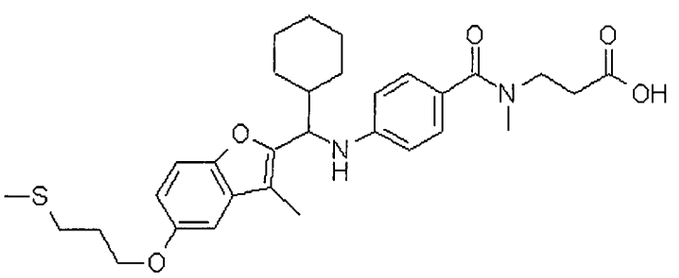
1568

metoxietoxi)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}amino]propanoato de etilo (0,62 g, 43%) en forma de un aceite amarillo. Esto se disolvió en etanol (5 mL), una solución acuosa 1 N de hidróxido de sodio (3,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a 50 °C durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (3,0 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (0,54 g, 91%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 2,13 (m, 12 H), 2,21 (s, 3 H), 2,66 (t, J = 5,7 Hz, 2 H), 3,46 (s, 3 H), 3,58 - 3,71 (m, 2 H), 3,76 (dd, J = 5,6, 4,1 Hz, 2 H), 4,14 (dd, J = 5,7, 4,1 Hz, 2 H), 4,38 (d, J = 7,9 Hz, 1 H), 6,57 - 6,65 (m, 3 H), 6,80 - 6,98 (m, 2 H), 7,22 - 7,26 (m, 1H), 7,53 (d, J = 8,7 Hz, 2 H).

Ejemplo A150

Ácido 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfanil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



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(1) ciclohexil{3-metil-5-[3-(metilsulfanil)propoxi]-1-benzofuran-2-il}metanona

Ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metanona (2,4 g) sintetizada en el Ejemplo A82(3) se disolvió en tetrahidrofurano (50 mL) y 2-(metiltio)propanol (1,0 mL), tributilfosfina (4,7 mL) y 1,1'-(azodicarbonil)dipiperidina (4,7 g) se añadieron a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 12 h. Hexano (50 mL) se añadió a la mezcla y el precipitado se filtró a través de celite. Se añadió agua al filtrado y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (3,1 g, 95%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,18 - 2,01 (m, 12 H), 2,14 (s, 3 H), 2,56 (s, 3 H), 2,72 (t, J = 7,2 Hz, 2 H), 3,25 - 3,40 (m, 1 H), 4,08 - 4,20 (m, 2 H), 7,03 - 7,42 (m, 3 H).

(2) ciclohexil{3-metil-5-[3-(metilsulfanil)propoxi]-1-benzofuran-2-il}metanol

Ciclohexil{3-metil-5-[3-(metilsulfanil)propoxi]-1-benzofuran-2-il}metanona (3,1 g) sintetizada en el punto (1) antes mencionado se disolvió en tetrahidrofurano (50 mL) y metanol (10 mL) y borohidruro de sodio (90%, 0,73 g) se añadió a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo, la mezcla de reacción se agitó a

1570

temperatura ambiente durante 1 h, luego se enfrió con hielo nuevamente y agua (5 mL) y ácido clorhídrico 1 N (25 mL) se añadieron cuidadosamente a la mezcla y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (3,0 g, 95%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,18 - 2,01 (m, 14 H), 2,13 (s, 3 H), 2,19 (s, 3 H), 2,72 (t, J = 7,2 Hz, 2 H), 4,11 (t, J = 7,2 Hz, 2 H), 4,40 - 4,55 (m, 1 H), 6,80 - 7,42 (m, 3 H).

(3) 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfanil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo

Ciclohexil{3-metil-5-[3-(metilsulfanil)propoxi]-1-benzofuran-2-il}metanol (1,5 g) sintetizado en el punto (2) antes mencionado se disolvió en tetrahidrofurano (10 mL) y el cloruro de tionilo (0,56 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (30 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-

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dimetilacetamida (10 mL), se añadieron yoduro de sodio (0,95 g), carbonato de sodio (0,63 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (1,1 g) sintetizado en el Ejemplo 2(2) a la solución y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (1,4 g, 56%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 2,00 (m, 17 H), 2,12 (s, 3 H), 2,21 (s, 3 H), 2,52 - 2,79 (m, 4 H), 3,01 (s, 3 H), 3,70 (t, J = 7,2 Hz, 2 H), 4,00 - 4,36 (m, 5 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,78 - 6,94 (m, 2 H), 7,14 - 7,25 (m, 3 H).

(4) ácido 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfanil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfanil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo (0,37 g) sintetizado en el punto (3) antes mencionado se disolvió en etanol (5 mL), solución acuosa 1 N de hidróxido de sodio (2,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a 50 °C durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (2,0 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada,

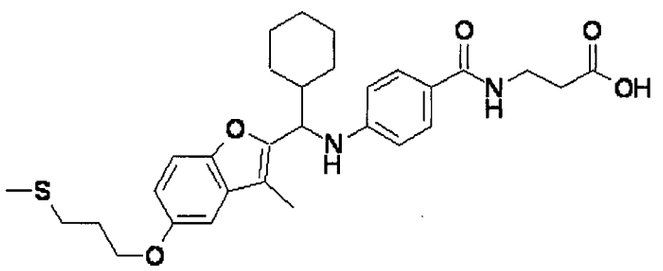
1572

se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (0,28 g, 79%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,89 - 2,10 (m, 14 H), 2,12 (s, 3 H), 2,21 (s, 3 H), 2,52 - 2,81 (m, 4 H), 3,04 (s, 3 H), 3,70 (q, J = 6,4 Hz, 2 H), 4,09 (t, J = 6,4 Hz, 2 H), 4,36 (d, J = 7,9 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,77 - 6,96 (m, 2 H), 7,20 - 7,26 (m, 3 H).

Ejemplo A151

Ácido 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfanil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoico




(1) 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfanil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoato de etilo

Ciclohexil{3-metil-5-[3-(metilsulfanil)propoxi]-1-benzofuran-2-il}metanol (1,5 g) sintetizado en el Ejemplo A150(2) se disolvió en tetrahidrofurano (10 mL) y cloruro de tionilo (0,56 mL) se añadió a la solución a temperatura

1573

ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (30 mL) se añadió cuidadosamente. La mezcla de reacción se agitó durante 10 min y se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilacetamida (10 mL), se añadieron yoduro de sodio (0,95 g), carbonato de sodio (0,63 g) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (1,0 g) sintetizado en el Ejemplo 1(2) a la solución y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (1,8 g, 77%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 2,00 (m, 17 H), 2,12 (s, 3 H), 2,21 (s, 3 H), 2,52 - 2,79 (m, 4 H), 3,66 (q J = 6,0 Hz, 2 H), 4,00 - 4,60 (m, 5 H), 6,56 (d, J = 8,9 Hz, 2 H), 6,58 (br. s. 1 H), 6,78 - 6,94 (m, 2 H), 7,20 - 7,60 (m, 3 H).

(2) ácido 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfanil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoico

3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfanil)propoxi]-1-benzofuran-2-

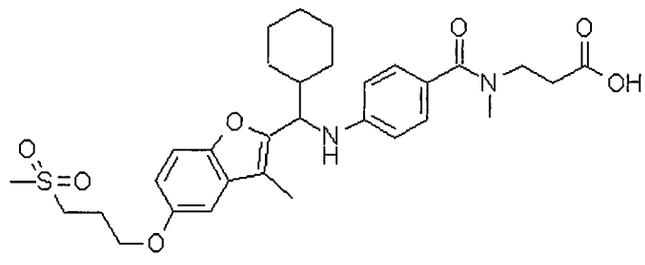
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il}metil)amino]fenil}carbonil)amino]propanoato de etilo (0,25 g) sintetizada en el punto (1) antes mencionado se disolvió en etanol (5 mL), solución acuosa 1 N de hidróxido de sodio (2,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a 50 °C durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (2,0 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (0,07 g, 31%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,82 - 2,16 (m, 14 H), 2,22 (s, 3 H), 2,52 - 2,81 (m, 4 H), 3,66 (q, J = 6,0 Hz, 2 H), 4,08 (t, J = 6,0 Hz, 2 H), 4,38 (d, J = 7,9 Hz, 1 H), 6,43 - 6,66 (m, 3 H), 6,74 - 6,96 (m, 2 H), 7,20 - 7,26 (m, 1 H), 7,53 (d, J = 8,9 Hz, 2 H).

Ejemplo A152

Ácido 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfonil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



1575

(1) 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfonil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo

El 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfanil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo (0,61 g) sintetizado en el Ejemplo A150(3) se disolvió en metanol (15 mL) y agua (2 mL), se añadió oxona (2,1 g) a la solución a temperatura ambiente y la mezcla se agitó durante 30 min. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con éter dietílico. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (0,48 g, 75%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 2,01 (m, 17 H), 2,21 (s, 3 H), 2,28 - 2,42 (m, 2 H), 2,61 (t, J = 6,9 Hz, 2 H), 2,95 (s, 3 H), 3,01 (s, 3 H), 3,20 - 3,36 (m, 2 H), 3,70 (t, J = 6,9 Hz, 2 H), 4,04 - 4,19 (m, 2 H), 4,26 - 4,44 (m, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,74 - 6,91 (m, 2 H), 7,15 - 7,25 (m, 3 H).

(2) ácido 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfonil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

El 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfonil)propoxi]-1-benzofuran-2-

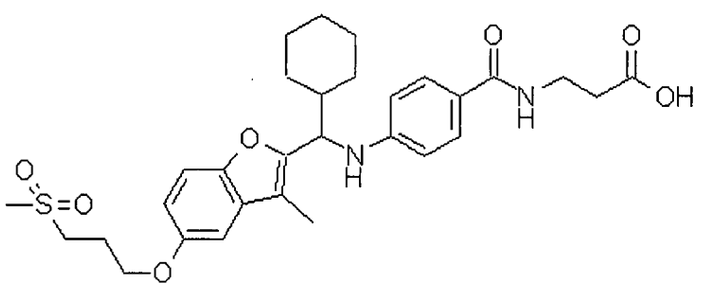
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il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo (0,48 g) sintetizado en el punto (1) antes mencionado se disolvió en etanol (5 mL), una solución acuosa 1 N de hidróxido de sodio (1,5 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a 50 °C durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (1,5 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (0,35 g, 78%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,87 - 2,15 (m, 12 H), 2,21 (s, 3 H), 2,25 - 2,45 (m, 2 H), 2,67 (br. s., 2 H), 2,95 (s, 3 H), 3,04 (s, 3 H), 3,17 - 3,36 (m, 2 H), 3,69 (t, J = 6,5 Hz, 2 H), 4,13 (t, J = 5,7 Hz, 2 H), 4,36 (d, J = 7,9 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,70 - 6,93 (m, 2 H), 7,16 - 7,26 (m, 3 H).

Ejemplo A153

Ácido 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfonil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoico



(1) 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfonil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoato de etilo

El 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfanil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoato de etilo (0,16 g) sintetizado en el Ejemplo A151(1) se disolvió en acetona (5 mL), el ácido metacloroperbenzoico (0,2 g) se añadió a la solución bajo enfriamiento con hielo y la mezcla se agitó durante 15 min. A la mezcla de reacción se añadió solución acuosa de sulfito de sodio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (0,11 g, 68%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,89 - 1,92 (m, 17 H), 2,22 (s, 3 H), 2,25 - 2,44 (m, 2 H), 2,58 (t, J = 5,8 Hz, 2 H), 2,95 (s, 3 H), 3,14 - 3,35 (m, 2 H), 3,66 (q, J = 6,8 Hz, 2 H), 4,13 (q, J = 7,2 Hz, 2 H), 4,38 (d, J = 7,9 Hz, 1 H), 6,43 - 6,64 (m, 3 H), 6,73 - 6,90 (m, 2 H), 7,16 - 7,25 (m, 1 H), 7,54 (d, J = 8,7 Hz, 2 H).

(2) ácido 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfonil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoico

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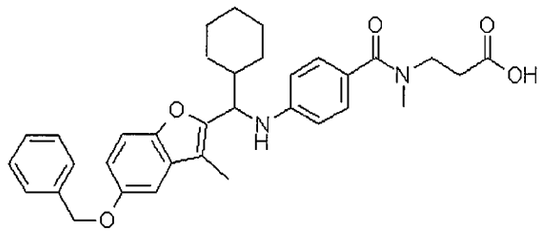
El 3-[({4-[(ciclohexil{3-metil-5-[3-(metilsulfonil)propoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoato de etilo (0,11 g) sintetizado en el punto (1) antes mencionado se disolvió en etanol (3 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a 50 °C durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (1,0 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (0,9 g, 80%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 2,14 (m, 14 H), 2,22 (s, 3 H), 2,26 - 2,42 (m, 2 H), 2,60 - 2,72 (m, 2 H), 2,95 (s, 3 H), 3,17 - 3,33 (m, 2 H), 3,66 (q, J = 5,7 Hz, 2 H), 4,13 (t, J = 5,7 Hz, 2 H), 4,38 (d, J = 7,9 Hz, 1 H), 6,47 - 6,62 (m, 3 H), 6,74 - 6,90 (m, 2 H), 7,20 - 7,26 (m, 1 H), 7,53 (d, J = 8,7 Hz, 2 H).

Ejemplo A154

Ácido 3-[{[4-({[5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoico

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(1) [5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metanol

La 1-[5-(benciloxi)-2-hidroxifenil]etanona (1,5 g) sintetizada en el Ejemplo A82(2) se disolvió en tetrahidrofurano (25 mL) y metanol (5 mL) y se añadió borohidruro de sodio (90%, 0,36 g) a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo, la mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se enfrió con hielo nuevamente y agua (5 mL) y ácido clorhídrico 1 N (10 mL) se añadieron cuidadosamente y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (1,4 g, 95%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,81 - 2,00 (m, 12 H), 2,18 (s, 3 H), 4,51 (d, J = 8,3 Hz, 1 H), 5,10 (s, 2 H), 6,87 - 7,06 (m, 2 H), 7,29 - 7,58 (m, 6 H).

(2) 3-[{[4-({[5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

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[5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metanol (1,5 g) sintetizada en el punto (1) antes mencionado se disolvió en tetrahidrofurano (20 mL) y cloruro de tionilo (0,57 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de hidrógeno-carbonato de sodio (30 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilacetamida (15 mL), se añadieron yoduro de sodio (0,98 g), carbonato de sodio (0,65 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (1,1 g) sintetizado en el Ejemplo 2(2) y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (1,8 g, 72%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 - 2,00 (m, 15 H), 2,21 (s, 3 H), 2,61 (t, J = 7,1 Hz, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,1 Hz, 2 H), 4,12 (q, J = 7,2 Hz, 2 H), 4,27 - 4,43 (m, 2 H), 5,08 (s, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,79 - 7,01 (m, 2 H), 7,13 - 7,24 (m, 3 H), 7,30 - 7,59 (m, 5 H).

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(3) ácido 3-[{[4-({[5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoico

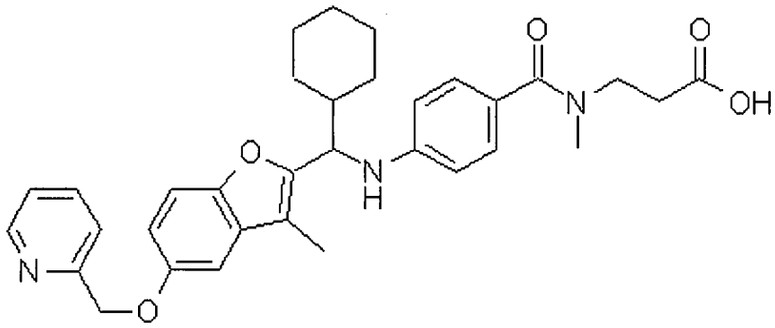
El 3-[{[4-({[5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,2 g) sintetizado en el punto (2) antes mencionado se disolvió en etanol (5 mL), una solución acuosa 1 N de hidróxido de sodio (1,5 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (1,5 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (0,18 g, 94%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,79 - 2,14 (m, 12 H), 2,21 (s, 3 H), 2,63 (t, J = 6,2 Hz, 2 H), 3,01 (s, 3 H), 3,68 (t, J = 6,2 Hz, 2 H), 4,36 (d, J = 7,9 Hz, 1 H), 5,08 (s, 2 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,80 - 7,03 (m, 2 H), 7,13 - 7,52 (m, 8 H).

Ejemplo A155

Ácido 3-[{[4-({ciclohexil[3-metil-5-(piridin-2-ilmetoxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

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(1) 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

El 3-[{[4-({[5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (2,46 g) sintetizado en el Ejemplo A154(2) se disolvió en etanol (50 mL) y se añadió óxido de platino (0,33 g) a la solución. La mezcla de reacción se agitó bajo una atmósfera de hidrógeno (1 atm) a temperatura ambiente durante la noche. La mezcla de reacción se filtró y el residuo se lavó con etanol. El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (1,64 g, 79%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 - 1,91 (m, 15 H), 2,18 (s, 3 H), 2,61 (t, J = 7,1 Hz, 2 H), 3,01 (s, 3 H), 3,71 (t, J = 7,1 Hz, 2 H), 4,02 - 4,18 (m, 2 H), 4,28 - 4,41 (m, 1 H), 4,86 (s, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,66 - 6,87 (m, 2 H), 7,14 - 7,25 (m, 3 H).

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(2) 3-[{[4-({ciclohexil[3-metil-5-(piridin-2-ilmetoxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

El 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,23 g) sintetizado en el punto (1) antes mencionado se disolvió en tetrahidrofurano (5 mL) y 2-piridinmetanol (62 mg), tributilfosfina (0,21 mL) y 1,1'-(azodicarbonil)dipiperidina (0,21 g) se añadieron a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo, la mezcla de reacción se agitó a temperatura ambiente durante 12 h, luego se añadió hexano (15 mL) a la mezcla y el precipitado se filtró a través de celite. Se añadió agua al filtrado y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (0,19 g, 70%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,88 - 1,95 (m, 15 H), 2,21 (s, 3 H), 2,54 - 2,72 (m, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,2 Hz, 2 H), 4,01 - 4,21 (m, 2 H), 4,22 - 4,54 (m, 1 H), 5,10 (s, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,80 - 7,05 (m, 2 H), 7,21 (d, J = 8,7 Hz, 2 H), 7,28 - 7,40 (m, 2 H), 7,79 (d, J = 8,0 Hz, 1 H), 8,58 (d, J = 4,5 Hz, 1 H), 8,70 (s, 1 H).

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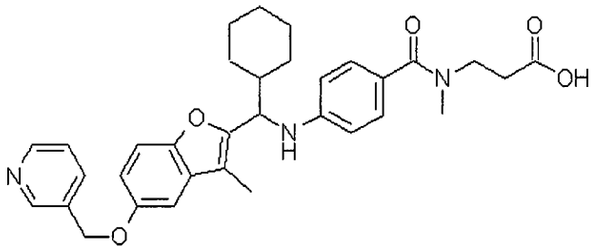
(3) ácido 3-[{[4-({ciclohexil[3-metil-5-(piridin-2-ilmetoxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

El 3-[{[4-({ciclohexil[3-metil-5-(piridin-2-ilmetoxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,19 g) sintetizado en el punto (2) antes mencionado se disolvió en etanol (5 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (1,0 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (0,11 g, 41%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 2,16 (m, 12 H), 2,20 (s, 3 H), 2,62 (br. s., 2 H), 3,02 (s, 3 H), 3,65 (br. s., 2 H), 4,34 (d, J = 7,9 Hz, 1 H), 5,15 (s, 2 H), 6,54 (d, J = 8,3 Hz, 2 H), 6,75 - 6,98 (m, 2 H), 7,11 - 7,30 (m, 4 H), 7,35 - 7,52 (m, 1 H), 7,93 (d, J = 7,9 Hz, 1 H), 8,50 - 8,70 (m, 2 H).

Ejemplo A156

Ácido 3-[{[4-({ciclohexil[3-metil-5-(piridin-3-ilmetoxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



(1) 3-[{[4-({ciclohexil[3-metil-5-(piridin-3-ilmetoxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

El 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,23 g) sintetizado en el Ejemplo A155(1) se disolvió en tetrahidrofurano (5 mL) y se añadieron 3-piridinmetanol (62 mg), tributilfosfina (0,21 mL) y 1,1'-(azodicarbonil)dipiperidina (0,21 g) a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo, la mezcla de reacción se agitó a temperatura ambiente durante 12 h, luego el hexano (5 mL) se añadió a la mezcla y el precipitado se filtró a través de celite. Se añadió agua al filtrado y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (0,13 g, 49%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 - 1,95 (m, 15 H), 2,19 (s, 3 H), 2,61 (br. s., 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,2 Hz,

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2 H), 4,12 (q, J = 7,2, 2,8 Hz, 2 H), 4,25 - 4,45 (m, 2 H), 5,24 (s, 2 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,84 - 7,02 (m, 2 H), 7,13 - 7,30 (m, 4 H), 7,55 (d, J = 7,9 Hz, 1 H), 7,67 - 7,82 (m, 1 H), 8,48 - 8,71 (m, 1 H).

(2) ácido 3-[{[4-({ciclohexil[3-metil-5-(piridin-3-ilmetoxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

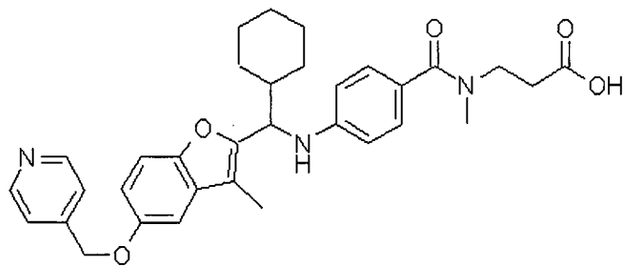
El 3-[{[4-({ciclohexil[3-metil-5-(piridin-3-ilmetoxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,13 g) sintetizado en el punto (1) antes mencionado se disolvió en etanol (5 mL), una solución acuosa 1 N de hidróxido de sodio (3,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (3,0 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (0,08 g, 95%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,83 - 2,13 (m, 12 H), 2,18 (s, 3 H), 2,50-2,75 (br. s., 2H), 3,01 (s, 3 H), 3,64 (br. s., 2 H), 4,35 (d, J = 7,9 Hz, 1 H), 5,44 (s, 2 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,79 - 7,09 (m, 2 H), 7,12 - 7,25 (m, 3 H), 7,45 - 8,01 (m, 3 H), 8,66 (br. s., 1 H).

Ejemplo A157

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Ácido 3-[{[4-({ciclohexil[3-metil-5-(piridin-4-ilmetoxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



(1) 3-[{[4-({ciclohexil[3-metil-5-(piridin-4-ilmetoxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

El 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,23 g) sintetizado en el Ejemplo A155(1) se disolvió en tetrahidrofurano (5 mL) y se añadieron 4-piridinmetanol (62 mg), tributilfosfina (0,21 mL) y 1,1'-(azodicarbonil)dipiperidina (0,21 g) a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo, la mezcla de reacción se agitó a temperatura ambiente durante 12 h, luego el hexano (5 mL) se añadió a la mezcla y el precipitado se filtró a través de celite. Se añadió agua al filtrado y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de

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etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (0,18 g, 64%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,89 - 1,97 (m, 15 H), 2,20 (s, 3 H), 2,61 (t, J = 7,2 Hz, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,2 Hz, 2 H), 4,06 - 4,18 (q, J = 7,2 Hz, 2 H), 4,74 (d, J = 4,0 Hz, 1 H), 5,11 (s, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,82 - 6,99 (m, 2 H), 7,14 - 7,31 (m, 3 H), 7,38 (d, J = 6,0 Hz, 2 H), 8,60 - 8,69 (m, 2 H).

(2) ácido 3-[{[4-({ciclohexil[3-metil-5-(piridin-4-ilmetoxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

El 3-[{[4-({ciclohexil[3-metil-5-(piridin-4-ilmetoxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,17 g) sintetizado en el punto (1) antes mencionado se disolvió en etanol (5 mL), una solución acuosa 1 N de hidróxido de sodio (3,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (3,0 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (0,13 g, 77%) en forma de un sólido amarillo pálido.

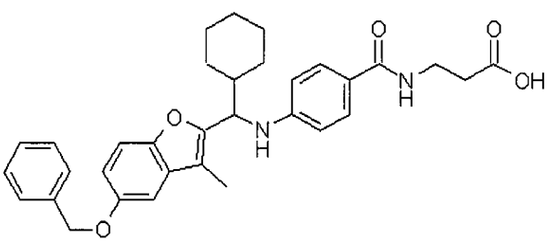
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,81 - 2,13 (m, 12 H), 2,19 (s, 3 H), 2,50-2,75 (br. s., 2H), 3,03 (s, 3 H), 3,60 - 3,75 (m,

1589

2 H), 4,34 (d, J = 7,9 Hz, 1 H), 5,16 (s, 2 H), 6,53 (d, J = 8,5 Hz, 2 H), 6,78 - 6,97 (m, 2 H), 7,12 - 7,31 (m, 3 H), 7,44 (d, J = 5,8 Hz, 2 H), 8,60 (d, J = 5,8 Hz, 2 H).

Ejemplo A158

Ácido 3-({[4-({[5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}amino)propanoico



(1) 3-({[4-({[5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}amino)propanoato de etilo

El [5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metanol (1,0 g) sintetizado en el Ejemplo A154(1) se disolvió en tetrahidrofurano (15 mL) y se añadió cloruro de tionilo (0,38 mL) a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de hidrógeno-carbonato de sodio (30 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilacetamida (20

1590

mL), yoduro de sodio (0,65 g), carbonato de sodio (0,43 g) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,68 g) sintetizado en el Ejemplo 1(2) se añadieron a la solución y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (0,78 g, 48%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 - 1,98 (m, 15 H), 2,21 (s, 3 H), 2,58 (t, J = 5,7 Hz, 2 H), 3,48 (q, J = 7,0 Hz, 1 H), 3,66 (q, J = 5,7 Hz, 2 H), 4,11 (q, J = 7,2 Hz, 2 H), 4,30 - 4,54 (m, 2 H), 5,08 (s, 2 H), 6,57 - 6,62 (m, 3 H), 6,82 - 7,02 (m, 2 H), 7,18 - 7,60 (m, 8 H).

(2) ácido 3-[{[4-({[5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoico

El 3-({[4-({[5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}amino)propanoato de etilo (0,78 g) sintetizado en el punto (1) antes mencionado se disolvió en etanol (5 mL), una solución acuosa 1 N de hidróxido de sodio (3,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (3,0 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio

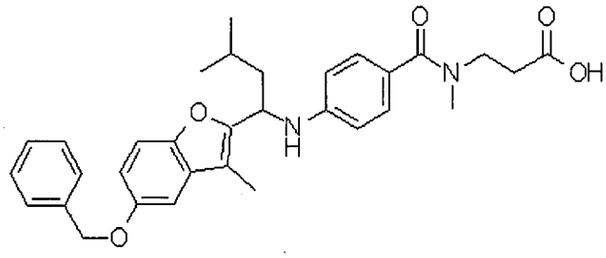
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y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (0,70 g, 94%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,81 - 2,10 (m, 12 H), 2,17 (s, 3 H), 2,50 (br. s., 2H), 3,55 (br. s., 2 H), 4,32 (br. s., 1 H), 5,04 (s, 2 H), 6,51 (d, J = 8,7 Hz, 2 H), 6,68 (br. s., 1 H), 6,81 - 6,99 (m, 2 H), 7,23 - 7,59 (m, 8 H).

Ejemplo A159

Ácido 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-3-metilbutil}amino)fenil]carbonil}(metil)amino]propanoico



(1) 5-(benciloxi)-3-metil-1-benzofuran-2-carboxilato de etilo

A una solución (200 mL) de 1-[5-(benciloxi)-2-hidroxifenil]etanona (15,3 g) sintetizado en el Ejemplo A82(1) en N,N-dimetilformamida se añadieron carbonato de potasio (13,1 g) y bromoacetato de etilo (7,7 mL) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con éter dietílico. El extracto se concentró a presión reducida, el residuo obtenido se disolvió en N,N-dimetilformamida (100 mL) nuevamente y se añadió 1,8-diazabiciclo[5,4,0]undec-7-eno (12,2 mL) a la solución. La

mezcla de reacción se agitó a 80 °C durante la noche. Tras enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción y la mezcla se extrajo con éter dietílico. El extracto se concentró a presión reducida y el sólido obtenido se lavó con etanol-éter isopropílico para dar el compuesto objeto del título (3,3 g, 17%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,44 (t, J = 7,2 Hz, 3 H), 2,55 (s, 3 H), 4,45 (q, J = 7,2 Hz, 2 H), 5,12 (s, 2 H), 7,01 - 7,21 (m, 2 H), 7,30 - 7,60 (m, 6 H).

(2) [5-(benciloxi)-3-metil-1-benzofuran-2-il]metanol

A una solución (50 mL) de 5-(benciloxi)-3-metil-1-benzofuran-2-carboxilato de etilo (3,3 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió hidruro de litio y aluminio (0,42 g) bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se enfrió con hielo nuevamente. Agua (1,1 mL), solución acuosa 1 N de hidróxido de sodio (5,5 mL) y agua (1,1 mL) se añadieron sucesivamente gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar el compuesto objeto del título (2,8 g, cuantitativo) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,70 - 1,90 (br. s., 1 H), 2,22 (s, 3 H), 4,73 (d, J = 6,0 Hz, 2 H), 5,10 (s, 2 H), 6,88 - 7,06 (m, 2 H), 7,28 - 7,56 (m, 6 H).

(3) 5-(benciloxi)-3-metil-1-benzofuran-2-carbaldehído

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A una solución (30 mL) de [5-(benciloxi)-3-metil-1-benzofuran-2-il]metanol (2,8 g) sintetizado en el punto (2) antes mencionado en tolueno se añadió dióxido de manganeso (5 g) y la mezcla se calentó a reflujo con una trampa de Dean-Stark durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, se filtró el catalizador a través de celite. El filtrado se concentró a presión reducida para dar el compuesto objeto del título (2,68 g, 94%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,58 (s, 3 H), 5,12 (s, 2 H), 7,06 - 7,25 (m, 2 H), 7,32 - 7,57 (m, 6 H), 10,00 (s, 1 H).

(4) 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-3-metilbutil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

A una solución (15 mL) de 5-(benciloxi)-3-metil-1-benzofuran-2-carbaldehído (1,2 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió gota a gota bromuro de isobutilmagnesio (1 M, solución de tetrahidrofurano) bajo enfriamiento con hielo. Se retiró el baño de hielo, la mezcla de reacción se agitó a temperatura ambiente durante 15 min y se añadió solución acuosa de cloruro de amonio para neutralizar la reacción. La mezcla de reacción se extrajo con acetato de etilo y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar 1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-3-metilbutan-1-ol (0,82 g, 56%) en forma de un aceite amarillo pálido. Esto se disolvió en tetrahidrofurano (15 mL) y el cloruro de tionilo

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(0,35 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y solución saturada acuosa de hidrógeno-carbonato de sodio (15 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilacetamida (15 mL), se añadieron yoduro de sodio (0,56 g), carbonato de sodio (0,38 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,63 g) sintetizado en el Ejemplo 2(2) a la solución y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (0,46 g, 33%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,76 - 1,05 (m, 6 H), 1,11 - 1,90 (m, 6 H), 2,24 (s, 3 H), 2,47 - 2,69 (m, 2 H), 3,01 (s, 3 H), 3,56 - 3,80 (m, 2 H), 3,95 - 4,32 (m, 3 H), 4,56 - 4,78 (m, 1 H), 5,09 (s, 2 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,80 - 7,02 (m, 2 H), 7,12 - 7,53 (m, 8 H).

(5) ácido 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-3-metilbutil}amino)fenil]carbonil}(metil)amino]propanoico

El 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-3-metilbutil}amino)fenil]carbonil}(metil)amino]propanoato de

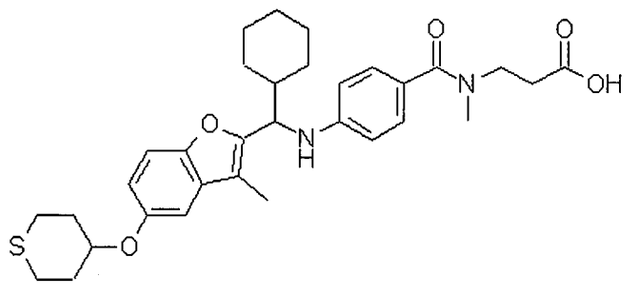
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etilo (0,46 g) sintetizado en el punto (4) antes mencionado se disolvió en etanol (5 mL), una solución acuosa 1 N de hidróxido de sodio (1,5 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (1,5 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se lavó con etanol-agua para dar el compuesto objeto del título (0,45 g, cuantitativo) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 (d, 3 H, J = 6,0 Hz), 0,99 (d, 3 H, J = 6,0 Hz), 1,25 - 2,00 (m, 4 H), 2,24 (s, 3 H), 2,67 (br. s., 2 H), 3,03 (s, 3 H), 3,71 (br. s., 2 H), 4,20 - 4,40 (m, 2 H), 5,08 (s, 2 H), 6,59 - 7,05 (m, 4 H), 7,31 - 7,57 (m, 8 H).

Ejemplo A160

Ácido 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-tiopiran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



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(1) 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-tiopiran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

El 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,50 g) sintetizado en el Ejemplo A155(1) se disolvió en tetrahidrofurano (10 mL) y tetrahidrotiopiran-4-ol (142 mg), tributilfosfina (0,45 mL) y 1,1'-(azodicarbonil)dipiperidina (0,45 g) se añadieron a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo, la mezcla de reacción se agitó a temperatura ambiente durante 12 h, luego el hexano (10 mL) se añadió a la mezcla y el precipitado se filtró a través de celite. Se añadió agua al filtrado y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (0,14 g, 23%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ 0,91 - 2,14 (m, 18 H), 2,20 (s, 3 H), 2,46 - 2,99 (m, 6 H), 3,01 (s, 3 H), 3,33 - 3,49 (m, 1 H), 3,70 (t, J = 7,1 Hz, 2 H), 4,12 (q, J = 7,2 Hz, 2 H), 4,25 - 4,40 (m, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,78 - 6,94 (m, 2 H), 7,16 - 7,30 (m, 3 H).

(2) ácido 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-tiopiran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

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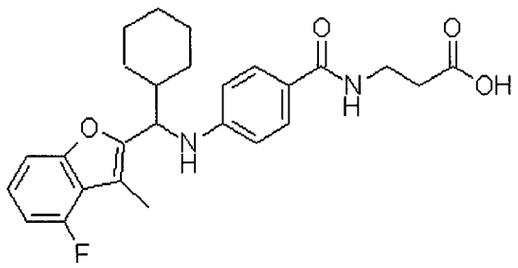
El 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-tiopiran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,14 g) sintetizado en el punto (1) antes mencionado se disolvió en etanol (3 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (1,0 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 3:1, relación en volumen) para dar el compuesto objeto del título (0,06 g, 46%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 - 2,15 (m, 16 H), 2,21 (s, 3 H), 2,41 - 2,95 (m, 6 H), 3,06 (s, 3 H), 3,72 (t, J = 6,4 Hz, 2 H), 4,21 - 4,46 (m, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,76 - 6,95 (m, 2 H), 7,22 - 7,26 (m, 3 H).

Ejemplo A161

Ácido 3-{[(4-{[ciclohexil(4-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico

1598



(1) ciclohexil(4-fluoro-3-metil-1-benzofuran-2-il)metanona

A una solución (50 mL) de 1-(2-fluoro-6-hidroxifenil)etanona (2,5 g) en N,N-dimetilformamida se añadieron carbonato de potasio (6,7 g) y 2-bromo-1-ciclohexiletanona (4,0 g) sintetizado en el Ejemplo A51(1) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y se filtró a través de celite. Se añadió agua al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo obtenido se disolvió en N,N-dimetilformamida (50 mL) nuevamente, el 1,8-diazabiciclo[5,4,0]undec-7-eno (2,6 mL) se añadió a la solución y la mezcla se agitó a 110 °C durante 1 h con calentamiento. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se neutralizó con ácido clorhídrico 1 N y la mezcla de reacción se extrajo con éter dietílico. El extracto se concentró a presión reducida y el compuesto precipitado se recristalizó en éter diisopropílico-hexano para dar el compuesto objeto del título (2,6 g, 62%) en forma de un sólido incoloro.

1S99

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,20 - 2,07 (m, 10 H), 2,73 (s, 3 H), 3,20 - 3,36 (m, 1 H), 6,92 (ddd, J = 10,0, 7,8, 0,8 Hz, 1 H), 7,27 - 7,44 (m, 2 H).

(2) ciclohexil(4-fluoro-3-metil-1-benzofuran-2-il)metanol

La ciclohexil(4-fluoro-3-metil-1-benzofuran-2-il)metanona (2,6 g) sintetizada en el punto (1) antes mencionado se disolvió en tetrahidrofurano (40 mL) y metanol (4 mL) y el borohidruro de sodio (90%, 0,83 g) se añadió a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo, la mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se enfrió con hielo nuevamente y agua (5 mL) y ácido clorhídrico 1 N (10 mL) se añadieron cuidadosamente a la mezcla y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (2,5 g, cuantitativo) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,72 - 2,22 (m, 12 H), 2,35 (s, 3 H), 4,50 (dd, J = 8,6, 6,1 Hz, 1 H), 6,86 (ddd, J = 10,1, 7,6, 1,3 Hz, 1 H), 7,11 - 7,24 (m, 2 H).

(3) ácido 3-{[(4-{[ciclohexil(4-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico

El ciclohexil(4-fluoro-3-metil-1-benzofuran-2-il)metanol (0,52 g) sintetizado en el punto (2) antes mencionado se disolvió en tetrahidrofurano (10 mL) y el cloruro de tionilo (0,27 mL) se añadió a la solución a temperatura ambiente. La

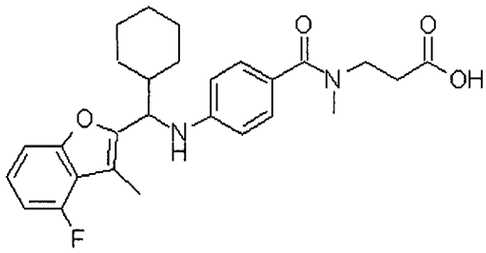
mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de hidrógeno-carbonato de sodio (5 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilacetamida (10 mL), se añadieron yoduro de sodio (0,45 g), carbonato de sodio (0,30 g) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,45 g) sintetizado en el Ejemplo 1(2) a la solución y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-{[(4-{[ciclohexil(4-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo (0,12 g, 13%) en forma de un aceite amarillo. El aceite obtenido se disolvió en etanol (3 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,11 g, 95%) en forma de un sólido incoloro.

1601

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 - 2,18 (m, 12 H), 2,37 (s, 3 H), 2,54 (t, J = 5,6 Hz, 2 H), 3,41 - 3,75 (m, 2 H), 4,35 (d, J = 8,1 Hz, 1 H), 6,44 - 6,64 (m, 3 H), 6,72 - 6,89 (m, 1 H), 7,02 - 7,19 (m, 2 H), 7,52 (d, J = 8,5 Hz, 2 H).

Ejemplo A162

Ácido 3-{[(4-{[ciclohexil(4-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




El ciclohexil(4-fluoro-3-metil-1-benzofuran-2-il)metanol (520 mg) sintetizado en el Ejemplo A161(2) se disolvió en tetrahidrofurano (10 mL) y cloruro de tionilo (0,27 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (10 mL) se añadió cuidadosamente a la mezcla. La mezcla se agitó durante 10 min y se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilacetamida (10 mL), se añadieron yoduro de sodio (0,45 g), carbonato de sodio (0,30 g) y 3-{[(4-

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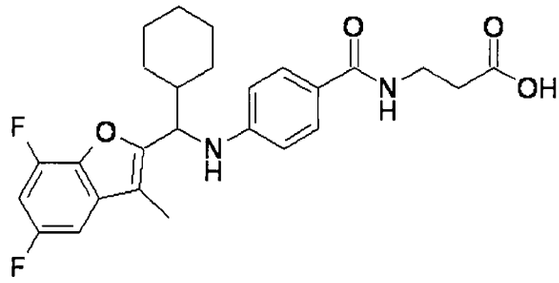
aminofenil)carbonil](metil)amino}propanoato de etilo (0,50 g) sintetizado en el Ejemplo 2(2) a la solución y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-{[(4-{[ciclohexil(4-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,15 g, 15%) en forma de un aceite amarillo. El aceite obtenido se disolvió en etanol (3 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,14 g, 95%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,88 - 2,16 (m, 12 H), 2,38 (s, 3 H), 2,65 (t, J = 6,4 Hz, 2 H), 3,03 (s, 3 H), 3,69 (t, J = 6,4 Hz, 2 H), 4,35 (d, J = 8,3 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,75 - 6,91 (m, 1 H), 7,03 - 7,18 (m, 2 H), 7,23 (d, J = 8,7 Hz, 2 H).

Ejemplo A163

Ácido 3-{[(4-{[ciclohexil(5,7-difluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico

1603



(1) ciclohexil(5,7-difluoro-3-metil-1-benzofuran-2-il)metanona

A una solución (50 mL) de 1-(3,5-difluoro-2-hidroxifenil)etanona (2,8 g) en N,N-dimetilformamida se añadieron carbonato de potasio (6,7 g) y 2-bromo-1-ciclohexiletanona (4,0 g) sintetizada en el Ejemplo A51(1) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y se filtró a través de celite. Se añadió agua al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo obtenido se disolvió en N,N-dimetilformamida (50 mL) nuevamente, el 1,8-diazabiciclo[5,4,0]undec-7-eno (2,6 mL) se añadió a la solución y la mezcla se agitó a 110 °C 1 h con calentamiento. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se neutralizó con ácido clorhídrico 1 N y la mezcla de reacción se extrajo con éter dietílico. El extracto se concentró a presión reducida y el compuesto precipitado se recristalizó en éter diisopropílico-hexano para dar el compuesto objeto del título (3,1 g, 70%) en forma de un sólido incoloro.

1004

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,09 - 2,09 (m, 10 H), 2,56 (s, 3 H), 3,17 - 3,47 (m, 1 H), 6,93 - 7,16 (m, 2 H).

(2) ciclohexil(5,7-difluoro-3-metil-1-benzofuran-2-il)metanol

La ciclohexil(5,7-difluoro-3-metil-1-benzofuran-2-il)metanona (3,1 g) sintetizada en el punto (1) antes mencionado se disolvió en tetrahidrofurano (50 mL) y metanol (5 mL) y el borohidruro de sodio (90%, 0,93 g) se añadió a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se enfrió con hielo nuevamente y agua (5 mL) y ácido clorhídrico 1 N (10 mL) se añadieron cuidadosamente a la mezcla y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (3,1 g, cuantitativo) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,83 - 2,00 (m, 12 H), 2,20 (s, 3 H), 4,52 (dd, J = 8,5, 6,8 Hz, 1 H), 6,79 - 6,93 (m, 2 H).

(3) ácido 3-{[(4-{[ciclohexil(5,7-difluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico

El ciclohexil(5,7-difluoro-3-metil-1-benzofuran-2-il)metanol (0,56 g) sintetizado en el punto (2) antes mencionado se disolvió en tetrahidrofurano (10 mL) y cloruro de tionilo (0,26 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una

1605

solución saturada acuosa de hidrógeno-carbonato de sodio (10 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilacetamida (10 mL), se añadieron yoduro de sodio (0,45 g), carbonato de sodio (0,30 g) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,45 g) sintetizado en el Ejemplo 1(2) a la solución y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-{[(4-{[ciclohexil(4-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,17 g, 17%) en forma de un aceite amarillo. El aceite obtenido se disolvió en etanol (3 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,16 g, 95%) en forma de un sólido incoloro.

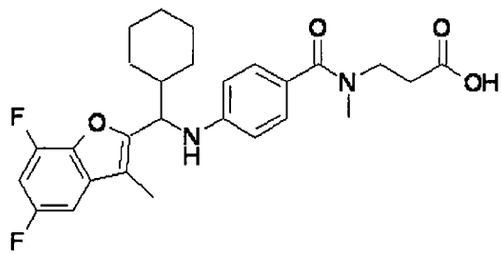
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,87 - 2,14 (m, 12 H), 2,21 (s, 3 H), 2,61 (t, J = 5,7 Hz, 2 H), 3,63 (q, J = 5,7 Hz, 2 H),

1606

4,39 (d, J = 8,3 Hz, 1 H), 6,45 - 6,64 (m, 3 H), 6,67 - 6,81 (m, 1 H), 6,87 (dd, J = 8,3, 2,3 Hz, 1 H), 7,53 (d, J = 8,7 Hz, 2 H).

Ejemplo A164

Ácido 3-{[(4-{[ciclohexil(5,7-difluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




El ciclohexil(5,7-difluoro-3-metil-1-benzofuran-2-il)metanol (0,56 g) sintetizado en el Ejemplo A163(2) se disolvió en tetrahidrofurano (10 mL) y el cloruro de tionilo (0,26 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (10 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilacetamida (10 mL), se añadieron yoduro de sodio (0,45 g), carbonato de sodio (0,30 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,50 g) sintetizado en el Ejemplo 2(2) a la solución y la mezcla se

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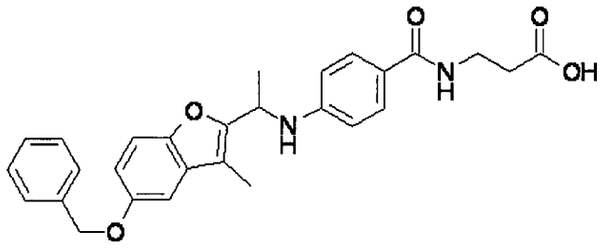
agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-{[(4-{[ciclohexil(4-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,17 g, 17%) en forma de un aceite amarillo. El aceite obtenido se disolvió en etanol (3 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,15 g, 93%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,88 - 2,16 (m, 12 H), 2,21 (s, 3 H), 2,67 (t, J = 6,4 Hz, 2 H), 3,04 (s, 3 H), 3,70 (t, J = 6,4 Hz, 2 H), 4,38 (d, J = 8,1 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,75 - 6,88 (m, 2 H), 7,23 (d, J = 8,7 Hz, 2 H).

Ejemplo A165

Ácido 3-({[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]etil}amino)fenil]carbonil}amino)propanoico

1608



(1) 1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]etanona

A una solución (120 mL) de 1-[5-(benciloxi)-2-hidroxifenil]etanona (6,4 g) sintetizada en el Ejemplo A82(1) en N,N-dimetilformamida se añadieron carbonato de potasio (10,8 g) y bromoacetona (4,8 g) a temperatura ambiente y la mezcla se agitó a 80 °C durante 1 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con éter dietílico. El extracto se concentró a presión reducida y el residuo obtenido se disolvió en N,N-dimetilformamida (120 mL) nuevamente y 1,8-diazabiciclo[5,4,0]undec-7-eno (5,1 mL) se añadió a la solución. La mezcla de reacción se agitó a 80 °C durante 2 h. Tras enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción y la mezcla se extrajo con éter dietílico. El extracto se concentró a presión reducida y el sólido obtenido se lavó con etanol-éter isopropílico para dar el compuesto objeto del título (2,5 g, 34%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,56 (s, 3 H), 2,60 (s, 3 H), 5,12 (s, 2 H), 7,11 (d, J = 2,3 Hz, 1 H), 7,17 (dd, J = 8,9, 2,3 Hz, 1 H), 7,30 - 7,55 (m, 6H).

(2) 1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]etanol

1609

La 1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]etanona (0,53 g) sintetizada en el punto (1) antes mencionado se disolvió en tetrahidrofurano (10 mL) y metanol (1 mL) y borohidruro de sodio (90%, 0,16 g) se añadió a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se enfrió con hielo nuevamente y agua (1 mL) y ácido clorhídrico 1 N (5 mL) se añadieron cuidadosamente a la mezcla y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un producto crudo (0,53 g, cuantitativo) del compuesto objeto del título en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,62 (d, J = 6,6 Hz, 3 H), 1,91 (br. s., 1 H), 2,21 (s, 3 H), 4,95 - 5,21 (m, 3 H), 6,87 - 7,07 (m, 2 H), 7,28 - 7,58 (m, 6 H).

(3) ácido 3-({[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]etil}amino)fenil]carbonil}amino)propanoico

1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]etanol (0,27 g) sintetizado en el punto (2) antes mencionado se disolvió en tetrahidrofurano (5 mL) y cloruro de tionilo (0,13 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (10 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se

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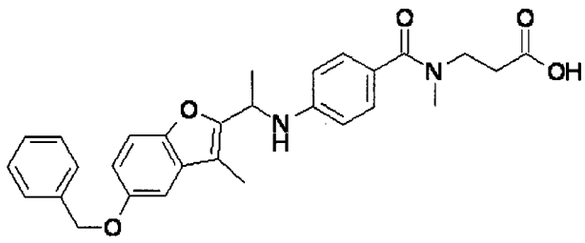
concentró a presión reducida. El residuo se disolvió en N,N-dimetilacetamida (10 mL), yoduro de sodio (0,21 g), carbonato de sodio (0,14 g) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,23 g) sintetizado en el Ejemplo 1(2) se añadieron a la solución y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-({[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]etil}amino)fenil]carbonil}amino)propanoato de etilo (0,15 g, 31%) en forma de un aceite amarillo. El aceite obtenido se disolvió en etanol (3 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,13 g, 88%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,62 (d, J = 7,0 Hz, 3 H), 2,22 (s, 3 H), 2,69 (d, J = 5,7 Hz, 2 H), 3,57 - 3,76 (m, 2 H), 4,65 - 4,88 (m, 1 H), 5,08 (s, 2 H), 6,59 - 6,75 (m, 3 H), 6,82 - 7,04 (m, 2 H), 7,29 - 7,62 (m, 8 H).

Ejemplo A166

1651

Ácido 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]etil}amino)fenil]carbonil}(metil)amino]propanoico



1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]etanol (0,27 g) sintetizado en el Ejemplo A165(2) se disolvió en tetrahidrofurano (5 mL) y el cloruro de tionilo (0,13 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (5 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilacetamida (10 mL), se añadieron yoduro de sodio (0,21 g), carbonato de sodio (0,14 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,24 g) sintetizado en el Ejemplo 2(2) a la solución y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel

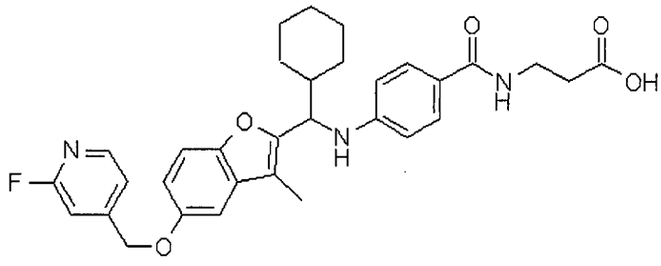
1612

de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-{[(4-{[ciclohexil(4-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,10 g, 20%) en forma de un aceite amarillo. El aceite obtenido se disolvió en etanol (3 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,09 g, 90%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,63 (d, J = 6,8 Hz, 3 H), 2,21 (s, 3 H), 2,69 (t, J = 6,5 Hz, 2 H), 3,05 (s, 3 H), 3,71 (t, J = 6,5 Hz, 2 H), 4,79 (q, J = 6,9 Hz, 1 H), 5,09 (s, 2 H), 6,60 (d, J = 8,3 Hz, 2 H), 6,84 - 7,02 (m, 2 H), 7,27 - 7,51 (m, 8 H).

Ejemplo A167

Ácido 3-[({4-[(ciclohexil{5-[(2-fluoropiridin-4-il)metoxi]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoico



1613

(1) 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo

El 3-[{[4-({[5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}amino]propanoato de etilo (5,6 g) sintetizado en el Ejemplo A158(1) se disolvió en etanol (100 mL) y óxido de platino (0,50 g) se añadió a la solución. La mezcla de reacción se agitó bajo una atmósfera de hidrógeno (1 atm) a temperatura ambiente durante la noche. La mezcla de reacción se filtró y el residuo se lavó con etanol. El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (3,2 g, 68%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 1,94 (m, 14 H), 2,16 (s, 3 H), 2,59 (t, J = 5,8 Hz, 2 H), 3,66 (q, J = 5,8 Hz, 2 H), 4,03 - 4,14 (m, 2 H), 4,26 - 4,56 (m, 2 H), 5,57 (br. s., 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,61 - 6,68 - 6,71 (m, 1 H), 6,73 (dd, J = 8,7, 2,3 Hz, 1 H), 6,83 (d, J = 2,3 Hz, 1 H), 7,19 (d, J = 8,7 Hz, 1 H), 7,55 (d, J = 8,7 Hz, 2 H).

(2) 3-[({4-[(ciclohexil{5-[(2-fluoropiridin-4-il)metoxi]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoato de etilo

El 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo (0,36 g) sintetizado en el punto (1) antes mencionado se disolvió en tetrahidrofurano (5 mL) y 2-fluoro-4-piridinmetanol (114

1614

mg), tributilfosfina (0,35 mL) y 1,1'-(azodicarbonil)dipiperidina (0,34 g) se añadieron a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo, la mezcla de reacción se agitó a temperatura ambiente durante 12 h, luego el hexano (5 mL) se añadió a la mezcla y el precipitado se filtró a través de celite. Se añadió agua al filtrado y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (0,23 g, 54%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 2,00 (m, 14 H), 2,22 (s, 3 H), 2,58 (t, J = 5,8 Hz, 2 H), 3,66 (q, J = 5,8 Hz, 2 H), 4,15 (q, J = 7,0 Hz, 2 H), 4,30 - 4,54 (m, 2 H), 5,13 (s, 2 H), 6,57 - 6,75 (m, 3 H), 6,83 - 6,96 (m, 2 H), 7,05 (s, 1 H), 7,18 - 7,32 (m, 2 H), 7,55 (d, J = 8,9 Hz, 2 H), 8,22 (d, J = 5,1 Hz, 1 H).

(3) ácido 3-[({4-[(ciclohexil{5-[(2-fluoropiridin-4-il)metoxi]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoico

El 3-[({4-[(ciclohexil{5-[(2-fluoropiridin-4-il)metoxi]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoato de etilo (0,24 g) sintetizado en el punto (2) antes mencionado se disolvió en etanol (3 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El

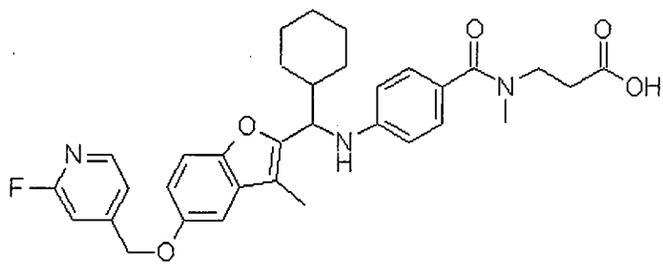
1615

etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,17 g, 75%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,83 - 2,13 (m, 12 H), 2,20 (s, 3 H), 2,52 - 2,77 (m, 2 H), 3,52 - 3,77 (m, 2 H), 4,38 (d, J = 8,0 Hz, 1 H), 5,14 (s, 2 H), 6,38 - 6,93 (m, 5 H), 7,04 (s, 1 H), 7,17 - 7,25 (m, 2 H), 7,53 (d, J = 8,7 Hz, 2 H), 8,21 (d, J = 5,3 Hz, 1 H).

Ejemplo A168

Ácido 3-[({4-[(ciclohexil{5-[(2-fluoropiridin-4-il)metoxi]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoico



(1) 3-[({4-[(ciclohexil{5-[(2-fluoropiridin-4-il)metoxi]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo

El 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metiletilo amino}fenil)carbonil](metil)amino}propanoato de (0,35 g) sintetizado en el Ejemplo A155(1) se disolvió en tetrahidrofurano (5 mL) y 2-fluoro-4-piridinmetanol (108 mg), tributilfosfina (0,32 mL) y 1,1'-(azodicarbonil)dipiperidina

1616

(0,32 g) se añadieron a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo, la mezcla de reacción se agitó a temperatura ambiente durante 12 h, luego se añadió hexano (5 mL) a la mezcla y el precipitado se filtró a través de celite. Se añadió agua al filtrado y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (0,27 g, 62%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δppm 0,94 - 1,99 (m, 14 H), 2,21 (s, 3 H), 2,61 (br. s., 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,1 Hz, 2 H), 4,12 (q, J = 7,0 H z, 2 H), 4,24 - 4,49 (m, 2 H), 5,14 (s, 2 H), 6,56 (d, J = 8,5 Hz, 2 H), 6,83 - 6,95 (m, 2 H), 7,06 (s, 1 H), 7,21 - 7,28 (m, 4 H), 8,22 (d, J = 5,1 Hz, 1 H).

(2) ácido 3-[({4-[(ciclohexil{5-[(2-fluoropiridin-4-il)metoxi]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)amino]propanoico

El 3-[({4-[(ciclohexil{5-[(2-fluoropiridin-4-il)metoxi]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo (0,27 g) sintetizado en el punto (1) antes mencionado se disolvió en etanol (3 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al

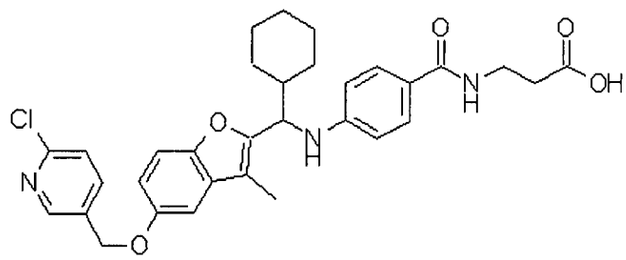
7617

residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,21 g, 82%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 - 2,14 (m, 12 H), 2,21 (s, 3 H), 2,67 (t, J = 6,4 Hz, 2 H), 3,04 (s, 3 H), 3,70 (t, J = 6,4 Hz, 2 H), 4,36 (d, J = 8,0 Hz, 1 H), 5,14 (s, 2 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,79 - 6,96 (m, 2 H), 7,05 (s, 1 H), 7,20 - 7,35 (m, 4 H), 8,21 (d, J = 5,3 Hz, 1 H).

Ejemplo A169

Ácido 3-{[(4-{[{5-[(6-cloropiridin-3-il)metoxi]-3-metil-1-benzofuran-2-il}(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico



(1) 3-{[(4-{[{5-[(6-cloropiridin-3-il)metoxi]-3-metil-1-benzofuran-2-il}(ciclohexil)metil]amino}fenil)carbonil]amino}propanoato de etilo

El 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo (0,35 g) sintetizado en el Ejemplo A167(1) se disolvió en tetrahidrofurano (5 mL) y 6-cloro-3-piridinmetanol (0,13 g), tributilfosfina (0,33 mL) y 1,1'-(azodicarbonil)dipiperidina

1618

(0,33 g) se añadieron a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo, la mezcla de reacción se agitó a temperatura ambiente durante 12 h, luego se añadió hexano (5 mL) a la mezcla y el precipitado se filtró a través de celite. Se añadió agua al filtrado y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (0,31 g, 65%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 2,13 (m, 14 H), 2,22 (s, 2 H), 2,58 (t, J = 5,9 Hz, 2 H), 3,65 (q, J = 5,9 Hz, 2 H), 4,25 (q, J = 7,0 Hz, 2 H), 4,29 - 4,54 (m, 1 H), 4,71 (d, J = 5,3 Hz, 1 H), 5,07 (s, 2 H), 6,48 - 6,68 (m, 3 H), 6,77 - 7,03 (m, 2 H), 7,25 (s, 1 H), 7,24 - 7,40 (m, 2 H), 7,54 (d, J = 8,7 Hz, 2 H), 7,68 - 7,76 (m, 1 H), 8,34 - 8,47 (m, 1 H).

(2) ácido 3-{[(4-{[{5-[(6-cloropiridin-3-il)metoxi]-3-metil-1-benzofuran-2-il}(ciclohexil)metil]amino}fenil)carbonil]amino}propanoico

El 3-{[(4-{[{5-[(6-cloropiridin-3-il)metoxi]-3-metil-1-benzofuran-2-il}(ciclohexil)metil]amino}fenil)carbonil]amino}propanoato de etilo (0,31 g) sintetizado en el punto (1) antes mencionado se disolvió en etanol (3 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al

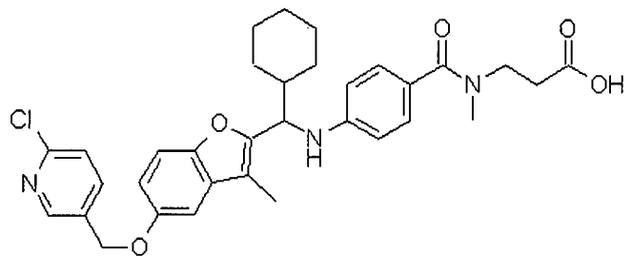
1619

residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,22 g, 74%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,88 - 2,13 (m, 12 H), 2,21 (s, 3 H), 2,62 (t, J = 5,7 Hz, 2 H), 3,45 - 3,77 (m, 2 H), 4,37 (d, J = 8,0 Hz, 1 H), 5,07 (s, 2 H), 6,43 - 6,64 (m, 3 H), 6,75 - 6,99 (m, 2 H), 7,23 - 7,26 (m, 1 H), 7,35 (d, J = 8,0 Hz, 1 H), 7,52 (d, J = 8,7 Hz, 2 H), 7,76 (dd, J = 8,0, 1,9 Hz, 1 H), 8,43 (d, J = 1,9 Hz, 1 H).

Ejemplo A170

Ácido 3-{[(4-{[{5-[(6-cloropiridin-3-il)metoxi]-3-metil-1-benzofuran-2-il}(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) 3-{[(4-{[{5-[(6-cloropiridin-3-il)metoxi]-3-metil-1-benzofuran-2-il}(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

El 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,39 g) sintetizado en el Ejemplo A155(1) se disolvió

1620

en tetrahidrofurano (5 mL), se añadieron 6-cloro-3-piridinmetanol (140 mg), tributilfosfina (0,35 mL) y 1,1'-(azodicarbonil)dipiperidina (0,36 g) a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo, la mezcla de reacción se agitó a temperatura ambiente durante 12 h, luego se añadió hexano (5 mL) a la mezcla y el precipitado se filtró a través de celite. Se añadió agua al filtrado y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (0,32 g, 66%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,95 - 2,13 (m, 14 H), 2,22 (s, 3H), 2,61 (t, J = 5,9 Hz, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 5,9 Hz, 2 H), 4,25 (q, J = 7,0 Hz, 2 H), 4,29 - 4,71 (m, 2 H), 5,07 (s, 2 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,77 - 7,03 (m, 2 H), 7,10 - 7,40 (m, 4 H), 7,68 - 7,76 (m, 1 H), 8,34 - 8,47 (m, 1 H).

(2) ácido 3-{[(4-{[{5-[(6-cloropiridin-3-il)metoxi]-3-metil-1-benzofuran-2-il}(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico

El 3-{[(4-{[{5-[(6-cloropiridin-3-il)metoxi]-3-metil-1-benzofuran-2-il}(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,32 g) sintetizado en el punto (1) antes mencionado se disolvió en etanol (3 mL), una solución acuosa

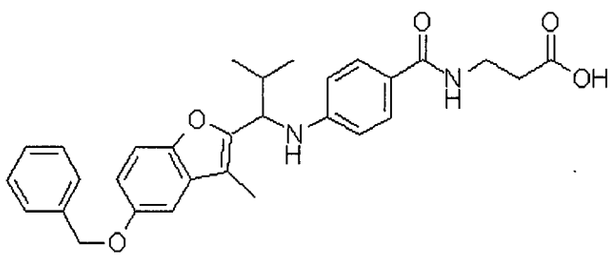
1621

1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,26 g, 85%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 - 2,15 (m, 12 H), 2,21 (s, 3 H), 2,52 - 2,77 (m, 2 H), 3,04 (s, 3 H), 3,69 (t, J = 6,4 Hz, 2 H), 4,36 (d, J = 8,0 Hz, 1 H), 5,08 (s, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,71 - 7,00 (m, 2 H), 7,14 - 7,26 (m, 3 H), 7,36 (d, J = 8,0 Hz, 1 H), 7,77 (dd, J = 8,0, 1,9 Hz, 1 H), 8,44 (d, J = 1,9 Hz, 1 H).

Ejemplo A171

Ácido 3-({[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}amino)propanoico




(1) 3-({[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}amino)propanoato de etilo

1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ol (1,0 g) sintetizado en el Ejemplo A85(2) se disolvió en tetrahidrofurano (15 mL) y el cloruro de tionilo (0,43 mL) se añadió a la solución a temperatura ambiente. La

1622

mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y solución saturada acuosa de carbonato ácido de sodio (15 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilacetamida (15 mL), se añadieron yoduro de sodio (0,74 g), carbonato de sodio (0,50 g) y 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (0,76 g) sintetizado en el Ejemplo 1(2) a la solución y la mezcla se agitó a 80 °C durante 12 h. Después de dejar enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (0,43 g, 25%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,4 Hz, 3 H), 1,12 (d, J = 7,0 Hz, 3 H), 1,25 (t, J = 7,0 Hz, 3 H), 2,16 - 2,34 (m, 4 H), 2,58 (t, J = 6,0 Hz, 2 H), 3,66 (q, J = 6,0 Hz, 2 H), 4,15 (q, J = 7,0 Hz, 2 H), 4,25 - 4,54 (m, 2 H), 5,08 (s, 2 H), 6,48 - 6,66 (m, 3 H), 6,80 - 7,04 (m, 2 H), 7,20 - 7,48 (m, 6 H), 7,55 (d, J = 9,0 Hz, 2 H).

(2) ácido 3-({[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}amino)propanoico

El 3-({[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}amino)propanoato de etilo

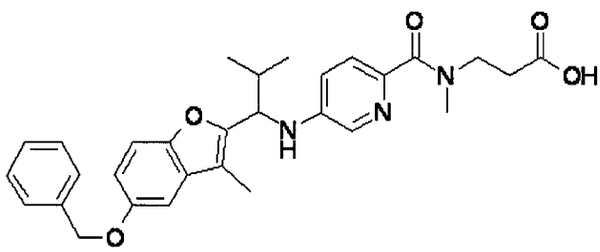
1623

(0,43 g) sintetizado en el punto (1) antes mencionado se disolvió en etanol (10 mL), solución acuosa 1 N de hidróxido de sodio (2,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (2,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,36 g, 89%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 (d, J = 6,4 Hz, 3 H), 1,13 (d, J = 6,4 Hz, 3 H), 2,10 - 2,40 (m, 4 H), 2,67 (br. s., 2 H), 3,66 (br. s., 2 H), 4,35 (br. s., 1 H), 5,08 (s., 2 H), 6,44 - 6,69 (m, 3 H), 6,79 - 7,68 (m, 10 H).

Ejemplo A172

Ácido 3-[{[5-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-2-il]carbonil}(metil)amino]propanoico



(1) 5-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-2-carboxilato de metilo

1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ol (1,0 g) sintetizado en el Ejemplo A58(2) se disolvió en tetrahidrofurano (15 mL) y el cloruro de tionilo

1624

(0,43 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (15 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilacetamida (15 mL), se añadieron yoduro de sodio (0,74 g), carbonato de sodio (0,50 g) y metil 5-aminopiridin-2-carboxilato de (0,50 g) a la solución y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (0,22 g, 15%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 (d, J = 6,8 Hz, 3 H), 1,15 (d, J = 6,8 Hz, 3 H), 2,16 - 2,40 (m, 4 H), 3,91 (s, 3 H), 4,35 (t, J = 8,1 Hz, 1 H), 4,65 (d, J = 8,7 Hz, 1 H), 5,08 (s, 2 H), 6,72 - 7,03 (m, 3 H), 7,18 - 7,53 (m, 6 H), 7,89 (d, J = 8,3 Hz, 1 H), 8,10 (d, J = 2,6 Hz, 1 H).

(2) 3-[{[5-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-2-il]carbonil}(metil)amino]propanoato de etilo

El 5-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-2-carboxilato de metilo (0,22 g)

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sintetizado en el punto (1) antes mencionado se disolvió en etanol (5 mL) y una solución acuosa 1 N de hidróxido de sodio (1 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a 70 °C durante 30 min, se dejó enfriar hasta temperatura ambiente y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilformamida (1 mL) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (0,17 g), monohidrato de 1-hidroxibenzotriazol (0,14 g) y 3-(metilamino)propanoato de etilo (0,10 g) se añadieron a la solución a temperatura ambiente y la mezcla se agitó durante la noche. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con éter dietílico. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (0,15 g, 56%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 (d, J = 6,4 Hz, 3 H), 1,14 (d, J = 6,4 Hz, 3 H), 1,26 (t, J = 7,2 Hz, 3 H), 2,16 - 2,36 (m, 4 H), 2,60 - 2,80 (m, 2 H), 3,80 (br. s., 2 H), 4,12 (q, J = 7,2 Hz, 2 H), 4,22 - 4,48 (m, 2 H), 5,09 (s, 2 H), 6,79 - 7,05 (m, 3 H), 7,24 - 7,51 (m, 7 H), 7,93 (br. s., 1 H).

(3) ácido 3-[{[5-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-2-il]carbonil}(metil)amino]propanoico

El 3-[{[5-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-2-il]carbonil}(metil)amino]propanoato de etilo (0,15 g)

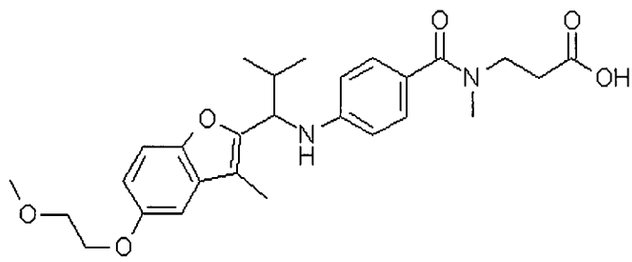
1686

sintetizado en el punto (2) antes mencionado se disolvió en etanol (3 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,14 g, cuantitativo) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 (d, J = 6,8 Hz, 3 H), 1,15 (d, J = 6,8 Hz, 3 H), 2,24 (s, 3 H), 2,27 - 2,39 (m, 1 H), 2,82 (br. s., 2 H), 3,10 (s, 3 H), 3,77 (t, J = 6,4 Hz, 2 H), 4,31 (d, J = 7,9 Hz, 1 H), 5,09 (s, 2 H), 6,85 - 7,03 (m, 3 H), 7,29 - 7,61 (m, 7 H), 8,04 (br. s., 1 H).

Ejemplo A173

Ácido 3-[{[4-({1-[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico



(1) 1-[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ona

A una solución (10 mL) de 1-[2-hidroxi-5-(2-metoxietoxi)fenil]etanona (0,55 g) sintetizado en el Ejemplo

(827

A79(1) en N,N-dimetilformamida se añadieron carbonato de potasio (1,1 g) y 1-bromo-3-metilbutan-2-ona (0,56 g) sintetizado en el Ejemplo A75(1) a temperatura ambiente y la mezcla se agitó durante 15 h. La mezcla de reacción se filtró a través de celite, se añadió agua (200 mL) y la mezcla se extrajo con éter dietílico (10 mL×2). El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilformamida (10 mL) y 1,8-diazabiciclo[5,4,0]undec-7-eno (0,41 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a 100 °C durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, ácido clorhídrico 1 N (10 mL) se añadió y la mezcla se extrajo con éter dietílico (10 mL×2). El extracto se lavó con agua, solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (0,71 g, 98%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,23 (d, J = 6,8 Hz, 6 H), 2,57 (s, 3 H), 3,48 (s, 3 H), 3,56 (quin, J = 6,8 Hz, 1 H), 3,74 - 3,85 (m, 2 H), 4,10 - 4,24 (m, 2 H), 7,05 (d, J = 2,6 Hz, 1 H), 7,14 (dd, J = 9,0, 2,6 Hz, 1 H), 7,39 (d, J = 9,0 Hz, 1 H).

(2)1-[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ol

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La 1-[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ona (0,71 g) sintetizada en el punto (1) antes mencionado se disolvió en tetrahidrofurano (5 mL) y metanol (0,5 mL) y el borohidruro de sodio (90%, 0,21 g) se añadió a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se enfrió con hielo nuevamente y agua (1 mL) y ácido clorhídrico 1 N (5 mL) se añadieron cuidadosamente a la mezcla y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un producto crudo (0,70 g, cuantitativo) del compuesto objeto del título en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,82 (d, J = 6,8 Hz, 3 H), 1,12 (d, J = 6,8 Hz, 3 H), 1,96 (br. s., 1 H), 2,12 - 2,33 (m, 4 H), 3,47 (s, 3 H), 3,70 - 3,85 (m, 2 H), 4,10 - 4,23 (m, 2 H), 4,46 (d, J = 8,3 Hz, 1 H), 6,79 - 7,01 (m, 2 H), 7,30 (d, J = 8,7 Hz, 1 H).

(3) ácido 3-[{[4-({1-[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico

El 1-[5-(2-Metoxietoxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ol (0,70 g) sintetizado en el punto (2) antes mencionado se disolvió en tetrahidrofurano (10 mL) y el cloruro de tionilo (0,34 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con

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hielo y una solución saturada acuosa de hidrógeno-carbonato de sodio (5 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (10 mL), yoduro de sodio (0,56 g), carbonato de sodio (0,38 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,63 g) sintetizado en el Ejemplo 2(2) se añadieron a la solución y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({1-[5-(2-metoxietoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,10 g, 8%) en forma de un aceite amarillo. El aceite obtenido se disolvió en etanol (3 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,05 g, 52%) en forma de un sólido incoloro.

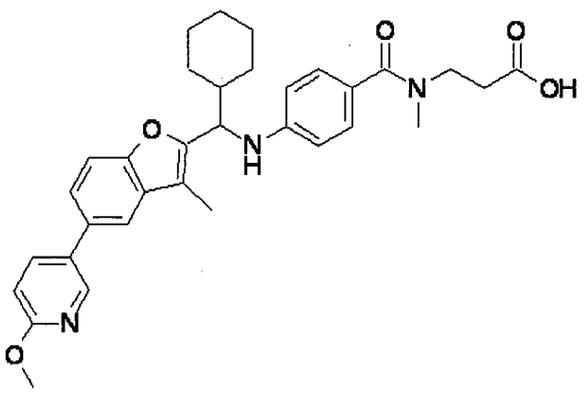
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,4 Hz, 3 H), 1,12 (d, J = 6,4 Hz, 3 H), 2,21 (s, 3 H), 2,23 - 2,36 (m, 1 H),

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2,67 (t, J = 6,4 Hz, 2 H), 3,04 (s, 3 H), 3,46 (s, 3 H), 3,69 (t, J = 6,4 Hz, 2 H), 3,73 - 3,84 (m, 2 H), 4,15 (dd, J = 5,7, 3,8 Hz, 2 H), 4,32 (d, J = 7,5 Hz, 1 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,76 - 6,98 (m, 2 H), 7,15 - 7,25 (m, 3 H).

Ejemplo A174

Ácido 3-[{[4-({ciclohexil[5-(6-metoxipiridin-3-il)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico




(1) (5-bromo-3-metil-1-benzofuran-2-il)(ciclohexil)metanona

1-[5-Bromo-2-hidroxifenil]etanona (13,4 g) se disolvió en N,N-dimetilformamida (300 mL). A la mezcla de reacción se añadieron carbonato de potasio (25,8 g) y 2-bromo-1-ciclohexiletanona (19,0 g) sintetizada en el Ejemplo A51(1) a temperatura ambiente y la mezcla se agitó durante 3 h. La mezcla de reacción se filtró a través de celite, se añadió agua (200 mL) y la mezcla se extrajo con éter dietílico (100 mL×2). El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilformamida (150 mL), 1,8-

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diazabiciclo[5,4,0]undec-7-eno (9,3 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a 100 °C durante 1 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, ácido clorhídrico 1 N (70 mL) se añadió y la mezcla se extrajo con éter dietílico (100 mL×2). El extracto se lavó con agua, solución saturada acuosa de carbonato ácido de sodio y salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El precipitado se lavó con éter diisopropílico para dar el compuesto objeto del título (15,4 g, 77%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,16 - 2,05 (m, 10 H), 2,56 (s, 3 H), 3,20 - 3,36 (m, 1 H), 7,40 (d, J = 8,9 Hz, 1 H), 7,55 (dd, J = 8,9, 1,5 Hz, 1 H), 7,77 (d, J = 1,5 Hz, 1 H).

(2) (5-bromo-3-metil-1-benzofuran-2-il)(ciclohexil)metanol

La (5-bromo-3-metil-1-benzofuran-2-il)(ciclohexil)metanona (7,5 g) sintetizada en el punto (1) antes mencionado se disolvió en tetrahidrofurano (100 mL) y metanol (15 mL) y el borohidruro de sodio (90%, 1,9 g) se añadió a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se enfrió con hielo nuevamente y agua (10 mL) y ácido clorhídrico 1 N (50 mL) se añadieron cuidadosamente a la mezcla y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un producto crudo (7,4 g,

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cuantitativo) del compuesto objeto del título en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,83 - 2,11 (m, 11 H), 2,19 (s, 3 H), 3,62 - 3,85 (m, 1 H), 4,51 (br. s., 1 H), 7,27 - 7,59 (m, 3 H).

(3) 3-{[(4-{[(5-bromo-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

El (5-bromo-3-metil-1-benzofuran-2-il)(ciclohexil)metanol (7,5 g) sintetizado en el punto (2) antes mencionado se disolvió en tetrahidrofurano (150 mL) y cloruro de tionilo (3,1 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y solución saturada acuosa de carbonato ácido de sodio (75 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (100 mL), se añadieron yoduro de sodio (5,2 g), carbonato de sodio (3,5 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (5,8 g) sintetizado en el Ejemplo 2(2) a la solución y la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1,

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relación en volumen) para dar el compuesto objeto del título (6,0 g, 47%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,88 - 1,97 (m, 14 H), 2,22 (s, 3 H), 2,61 (t, J = 7,1 Hz, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,1 Hz, 2 H), 3,99 - 4,17 (m, 2 H), 4,23 - 4,47 (m, 2 H), 6,55 (d, J = 8,7 Hz, 2 H), 7,11 - 7,37 (m, 4 H), 7,54 (d, J = 1,7 Hz, 1 H).

(4) ácido 3-[{[4-({ciclohexil[5-(6-metoxipiridin-3-il)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (5 mL) de 3-{[(4-{[(5-bromo-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,25 g) sintetizado en el punto (3) antes mencionado en N,N-dimetilacetamida se añadieron ácido (6-metoxipiridin-3-il)borónico (0,14 g), carbonato de potasio (0,13 g) y tetrakistrifenilfosfina paladio (0,05 g) y la mezcla se agitó a 90 °C durante 12 h bajo una atmósfera de nitrógeno. La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró a través de celite y el residuo se lavó con éter dietílico. Se añadió agua al filtrado y la capa orgánica se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[5-(6-metoxipiridin-3-il)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,15 g, 58%) en forma de un aceite amarillo pálido. El

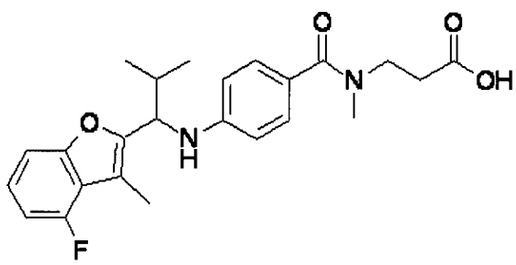
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aceite obtenido se disolvió en etanol (1 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,12 g, 85%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,27 - 2,19 (m, 12 H), 2,29 (s, 3 H), 2,69 (t, J = 6,4 Hz, 2 H), 3,05 (s, 3 H), 3,70 (t, J = 6,4 Hz, 2 H), 3,99 (s, 3 H), 4,41 (d, J = 7,9 Hz, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 6,83 (d, J = 9,0 Hz, 1 H), 7,19 - 7,26 (m, 2 H), 7,32 - 7,53 (m, 3 H), 7,81 (dd, J = 8,5, 2,4 Hz, 1 H), 8,38 (d, J = 2,3 Hz, 1 H).

Ejemplo A175

Ácido 3-{[(4-{[1-(4-fluoro-3-metil-1-benzofuran-2-il)-2-metilpropil]amino}fenil)carbonil](metil)amino}propanoico




(1) 1-(4-fluoro-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ona

A una solución (25 mL) de 1-(2-fluoro-6-hidroxifenil)etanona (1,3 g) en N,N-dimetilformamida se

añadieron carbonato de potasio (3,5 g) y 1-bromo-3-metilbutan-2-ona (1,7 g) sintetizada en el Ejemplo A75(1) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y se filtró a través de celite. Se añadió agua al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo obtenido se disolvió en N,N-dimetilformamida (15 mL) nuevamente, 1,8-diazabiciclo[5,4,0]undec-7-eno (1,3m) se añadió a la mezcla y la mezcla se agitó a 110 °C durante 1 h con calentamiento. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se neutralizó con ácido clorhídrico 1 N y la mezcla se extrajo con éter dietílico. El extracto se concentró a presión reducida y el compuesto precipitado se recristalizó en éter diisopropílico-hexano para dar el compuesto objeto del título (1,4 g, 77%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,24 (d, J = 6,8 Hz, 6 H), 2,74 (s, 3 H), 3,50 - 3,66 (m, 1 H), 6,93 (dd, J = 10,2, 7,9 Hz, 1 H), 7,28 - 7,50 (m, 2 H).

(2) 1-(4-fluoro-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ol

La 1-(4-fluoro-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ona (1,4 g) sintetizada en el punto (1) antes mencionado se disolvió en tetrahidrofurano (20 mL) y metanol (2 mL) y el borohidruro de sodio (90%, 0,53 g) se añadió a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1

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h, luego se enfrió con hielo nuevamente y agua (2 mL) y ácido clorhídrico 1 N (5 mL) se añadieron cuidadosamente a la mezcla y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un producto crudo (1,4 g, cuantitativo) del compuesto objeto del título en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,82 (d, J = 6,8 Hz, 3 H), 1,13 (d, J = 6,8 Hz, 3 H), 1,99 (d, J = 5,7 Hz, 1 H), 2,22 (dt, J = 8,3, 6,8 Hz, 1 H), 2,36 (s, 3 H), 4,46 (dd, J = 8,3, 5,7 Hz, 1 H), 6,77 - 7,23 (m, 3 H).

(3) ácido 3-{[(4-{[1-(4-fluoro-3-metil-1-benzofuran-2-il)-2-metilpropil]amino}fenil)carbonil](metil)amino}propanoico

El 1-(4-fluoro-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ol (1,4 g) sintetizado en el punto (2) antes mencionado se disolvió en tetrahidrofurano (20 mL) y cloruro de tionilo (0,84 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y solución saturada acuosa de carbonato ácido de sodio (20 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (30 mL), yoduro de sodio (1,4 g), carbonato de sodio (0,96 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (1,6 g) sintetizado en el Ejemplo 2(2) se añadieron a la solución y

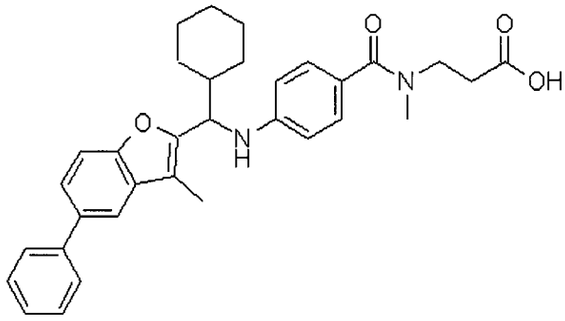
la mezcla se agitó a 80 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-{[(4-{[1-(4-fluoro-3-metil-1-benzofuran-2-il)-2-metilpropil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,20 g, 7%) en forma de un aceite amarillo. El aceite obtenido se disolvió en etanol (2 mL), solución acuosa 1 N de hidróxido de sodio (2,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (2,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,06 g, 32%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 (d, J = 6,4 Hz, 3 H), 1,14 (d, J = 6,4 Hz, 3 H), 2,09 - 2,32 (m, 1 H), 2,39 (s, 3 H), 2,69 (t, J = 6,2 Hz, 2 H), 3,05 (s, 3 H), 3,71 (t, J = 6,2 Hz, 2 H), 4,31 (d, J = 7,9 Hz, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 6,76 - 7,19 (m, 3 H), 7,25 (d, J = 8,7 Hz, 2 H).

Ejemplo A176

Ácido 3-{[(4-{[ciclohexil(3-metil-5-fenil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

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A una solución (5 mL) de 3-{[(4-{[(5-bromo-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,28 g) sintetizado en el Ejemplo A174(3) en N,N-dimetilacetamida se añadieron ácido fenilborónico (0,12 g), carbonato de potasio (0,14 g) y tetrakistrifenilfosfina paladio (0,10 g) y la mezcla se agitó a 70 °C durante 12 h bajo una atmósfera de nitrógeno. La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró a través de celite y el residuo se lavó con éter dietílico. Se añadió agua al filtrado y la capa orgánica se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-{[(4-{[ciclohexil(3-metil-5-fenil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,15 g, 54%) en forma de un aceite amarillo pálido. El aceite obtenido se disolvió en etanol (1 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió

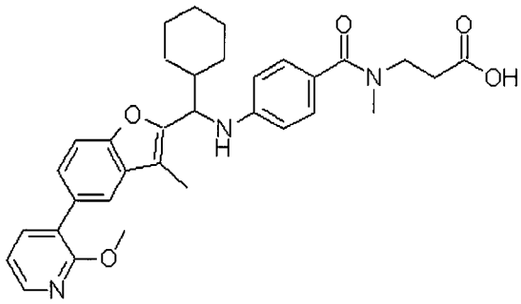
1639

al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,09 g, 67%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 - 2,16 (m, 11 H), 2,29 (s, 3 H), 2,69 (t, J = 6,2 Hz, 2 H), 3,05 (s, 3 H), 3,72 (t, J = 6,2 Hz, 2 H), 4,41 (d, J = 7,9 Hz, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 7,23 - 7,66 (m, 10 H).

Ejemplo A177

Ácido 3-[{[4-({ciclohexil[5-(2-metoxipiridin-3-il)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



A una solución (15 mL) de 3-{[(4-{[(5-bromo-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,53 g) sintetizado en el Ejemplo A174(3) en N,N-dimetilacetamida se añadieron ácido (2-metoxipiridin-3-il)borónico (0,29 g), carbonato de potasio (0,27 g) y tetrakistrifenilfosfina paladio (0,05 g) y la mezcla se agitó a 90 °C durante 12 h bajo una atmósfera de nitrógeno. La mezcla de reacción se enfrió hasta temperatura ambiente y se

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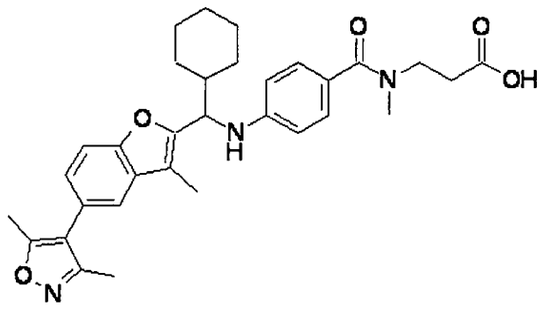
filtró a través de celite y el residuo se lavó con éter dietílico. Se añadió agua al filtrado y la capa orgánica se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[5-(2-metoxipiridin-3-il)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,50 g, 89%) en forma de un aceite amarillo pálido. El aceite obtenido se disolvió en etanol (1 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,47 g, cuantitativo) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,97 - 2,15 (m, 11 H), 2,27 (s, 3 H), 2,49 - 2,65 (m, 2 H), 2,99 (s, 3 H), 3,65 (br. s., 2 H), 3,95 (s, 3 H), 4,39 (d, J = 7,9 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,97 (dd, J = 7,2, 4,9 Hz, 1 H), 7,23 (d, J = 8,7 Hz, 2 H), 7,38 - 7,66 (m, 4 H), 8,15 (dd, J = 5,1, 2,1 Hz, 1 H).

Ejemplo A178

Ácido 3-[{[4-({ciclohexil[5-(3,5-dimetilisoxazol-4-il)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

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A una solución (15 mL) de 3-{[(4-{[(5-bromo-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,54 g) sintetizado en el Ejemplo A174(3) en tolueno se añadieron ácido (3,5-dimetilisoxazol-4-il)borónico (0,41 g) y solución acuosa 2 N de carbonato de sodio (1,46 mL) y la mezcla se agitó a temperatura ambiente durante 10 min bajo una atmósfera de argón. A la mezcla de reacción se añadieron 2-diciclohexilfosfino-2',6'-dimetoxibifenilo (0,05 g) y tris(dibencilidenacetona)dipaladio (0) (0,03 g) y la mezcla se calentó a reflujo bajo una atmósfera de argón durante la noche. La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró a través de celite y el residuo se lavó con éter dietílico. Se añadió agua al filtrado y la capa orgánica se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar etil 3-[{[4-({ciclohexil[5-(3,5-dimetilisoxazol-4-il)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de (0,13 g, 23%) en forma de un aceite amarillo pálido. El

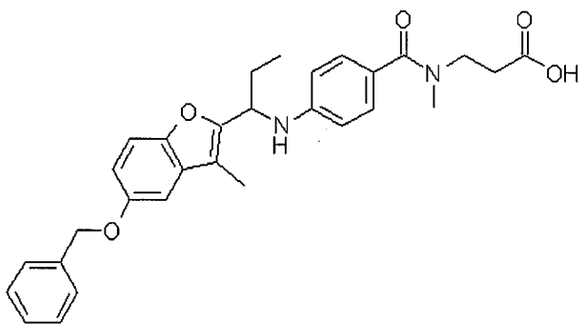
1642

aceite obtenido se disolvió en etanol (1 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,12 g, 96%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 2,19 (m, 11 H), 2,26 (s, 3 H), 2,27 (s, 3 H), 2,39 (s, 3 H), 2,71 (t, J = 6,2 Hz, 2 H), 3,07 (s, 3 H), 3,73 (t, J = 6,2 Hz, 2 H), 4,41 (d, J = 7,9 Hz, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 7,08 (dd, J = 8,3, 1,5 Hz, 1 H), 7,20 - 7,26 (m, 3 H), 7,42 (d, J = 8,3 Hz, 1 H).

Ejemplo A179

Ácido 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]propil}amino)fenil]carbonil}(metil)amino]propanoico




(1) 1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]propan-1-ona

A una solución (150 mL) de 1-[5-(benciloxi)-2-hidroxifenil]etanona (7,8 g) sintetizada en el Ejemplo 82(1)

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en N,N-dimetilformamida se añadieron carbonato de potasio (13,2 g) y 1-bromobutan-2-ona (5,0 mL) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y se filtró a través de celite. Se añadió agua al filtrado y la mezcla se extrajo con éter dietílico. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo obtenido se disolvió en N,N-dimetilformamida (100 mL) nuevamente, el 1,8-diazabiciclo[5,4,0]undec-7-eno (4,9 mL) se añadió a la solución y la mezcla se agitó a 110 °C con calentamiento durante 1 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se neutralizó con ácido clorhídrico 1 N y la mezcla se extrajo con éter dietílico. El extracto se concentró a presión reducida y el compuesto precipitado se recristalizó en éter diisopropílico-hexano para dar el compuesto objeto del título (6,2 g, 66%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,22 (t, J = 7,2 Hz, 3 H), 2,57 (s, 3 H), 3,01 (q, J = 7,2 Hz, 2 H), 5,12 (s, 2 H), 7,04 - 7,52 (m, 8 H).

(2) 1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]propan-1-ol

La 1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]propan-1-ona (0,88 g) sintetizada en el punto (1) antes mencionado se disolvió en tetrahidrofurano (15 mL) y metanol (1 mL) y el borohidruro de sodio (90%, 0,25 g) se añadió a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1

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h, luego se enfrió con hielo nuevamente y agua (2 mL) y ácido clorhídrico 1 N (5 mL) se añadieron cuidadosamente a la mezcla y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un producto crudo (0,85 g, cuantitativo) del compuesto objeto del título en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 (t, J = 7,4 Hz, 3 H), 1,92 - 2,03 (m, 3 H), 2,21 (s, 3 H), 4,69 - 4,87 (m, 1 H), 5,11 (s, 2 H), 6,89 - 7,51 (m, 8 H).

(3) Ácido 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]propil}amino)fenil]carbonil}(metil)amino]propanoico

El 1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]propan-1-ol (0,85 g) sintetizado en el punto (2) antes mencionado se disolvió en tetrahidrofurano (15 mL) y cloruro de tionilo (0,40 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y solución saturada acuosa de carbonato ácido de sodio (20 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (15 mL), se añadieron yoduro de sodio (0,67 g), carbonato de sodio (0,45 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,75 g) sintetizado en el Ejemplo 2(2) a la solución y la mezcla se agitó a 80 °C durante 4 h. Después de enfriar, se añadió agua

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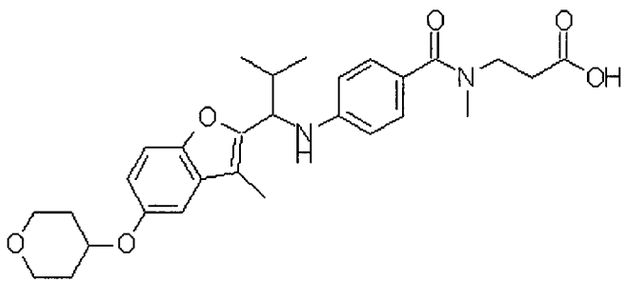
a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]propil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,15 g, 9%) en forma de un aceite amarillo. El aceite obtenido se disolvió en etanol (2 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,10 g, 71%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 (t, J = 7,3 Hz, 3 H), 1,87 - 2,08 (m, 2 H), 2,23 (s, 3 H), 2,66 (t, J = 6,2 Hz, 2 H), 3,03 (s, 3 H), 3,70 (t, J = 6,2 Hz, 2 H), 4,52 (dd, J = 8,3, 6,2 Hz, 1 H), 5,09 (s, 2 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,82 - 7,02 (m, 2 H), 7,18 - 7,51 (m, 8 H).

Ejemplo A180

Ácido 3-(metil{[4-({2-metil-1-[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]propil}amino)fenil]carbonil}amino)propanoico

1646



(1) 1-(5-hidroxi-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ona

A una solución de 1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ona (11,4 g) sintetizado en el Ejemplo A85(1) en etanol (200 mL) se añadió complejo de carbono de paladio-etilendiamina (1,1 g) a temperatura ambiente. La mezcla de reacción se agitó bajo una atmósfera de hidrógeno (1 atm) a temperatura ambiente durante 16 h y el catalizador se filtró. El filtrado se concentró a presión reducida para dar un producto crudo (8,0 g, cuantitativo) del compuesto objeto del título en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,24 (d, J = 6,8 Hz, 6 H), 2,55 (s, 3 H), 3,48 - 3,63 (m, 1 H), 6,95 - 7,40 (m, 3 H).

(2) ácido 3-(metil{[4-({2-metil-1-[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]propil}amino)fenil]carbonil}amino)propanoico

La 1-(5-hidroxi-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ona (1,1 g) sintetizada en el punto (1) antes mencionado se disolvió en tetrahidrofurano (15 mL) y metanol (1 mL) y el borohidruro de sodio (90%, 0,30 g) se añadió a la solución bajo enfriamiento con hielo. Se retiró el baño de

hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se enfrió con hielo nuevamente y agua (5 mL) y ácido clorhídrico 1 N (15 mL) se añadieron cuidadosamente a la mezcla y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar 1-(5-hidroxi-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ol (0,71 g, 65%) en forma de un aceite amarillo pálido. El aceite obtenido se disolvió en tetrahidrofurano (15 mL) y cloruro de tionilo (0,30 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y solución saturada acuosa de carbonato ácido de sodio (20 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (15 mL), se añadieron yoduro de sodio (0,52 g), carbonato de sodio (0,35 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,58 g) sintetizado en el Ejemplo 2(2) a la mezcla y la mezcla se agitó a 70 °C durante 4 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-(metil{[4-({2-metil-1-[3-metil-5-(tetrahidro-2H-

1648

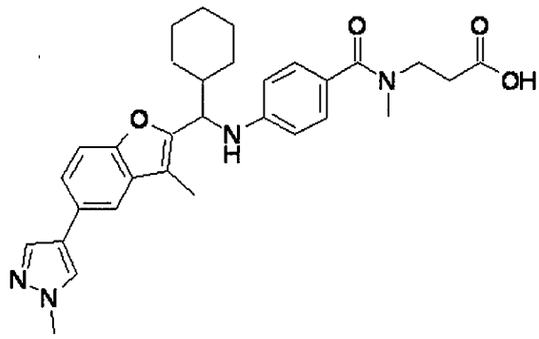
piran-4-iloxi)-1-benzofuran-2-il]propil}amino)fenil]carbonil}amino)propanoato de etilo (0,54 g, 46%) en forma de un aceite amarillo. El aceite obtenido se disolvió en etanol (3 mL), una solución acuosa 1 N de hidróxido de sodio (3,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (3,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,53 g, 98%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 (d, J = 6,8 Hz, 3 H), 1,13 (d, J = 6,8 Hz, 3 H), 1,70 - 2,09 (m, 4 H), 2,21 (s, 3 H), 2,22 - 2,27 (m, 1 H), 2,67 (t, J = 6,2 Hz, 2 H), 3,04 (s, 3 H), 3,56 (ddd, J = 11,5, 8,5, 3,4 Hz, 2 H), 3,70 (t, J = 6,2 Hz, 2 H), 3,91 - 4,08 (m, 2 H), 4,32 (d, J = 7,6 Hz, 1 H), 4,43 (tt, J = 7,9, 3,8 Hz, 1 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,85 (dd, J = 8,7, 2,7 Hz, 1 H), 6,93 (d, J = 2,3 Hz, 1 H), 7,19 - 7,26 (m, 3 H).

Ejemplo A181

Ácido 3-[{[4-({ciclohexil[3-metil-5-(1-metil-1H-pirazol-4-il)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

1649



A una solución (15 mL) de 3-{[(4-{[(5-bromo-3-metil-1-benzofuran-2-il)(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,59 g) sintetizado en el Ejemplo A174(3) en N,N-dimetilacetamida se añadieron 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (0,44 g), carbonato de potasio (0,29 g) y tetrakistrifenilfosfina paladio (0,06 g) y la mezcla se agitó a 70 °C durante 24 h bajo una atmósfera de argón. La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró a través de celite y el residuo se lavó con éter dietílico. Se añadió agua al filtrado y la capa orgánica se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[3-metil-5-(1-metil-1H-pirazol-4-il)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,23 g, 39%) en forma de un aceite amarillo pálido. El aceite obtenido se disolvió en etanol (1 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a

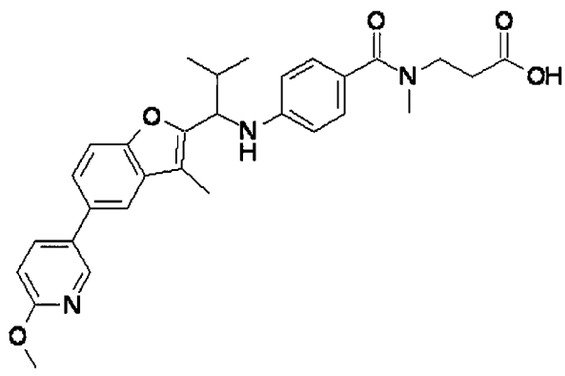
1850

temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,04 g, 16%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 2,11 (m, 11 H), 2,27 (s, 3 H), 2,67 (br. s., 2 H), 3,03 (s, 3 H), 3,70 (t, J = 6,2 Hz, 2 H), 3,94 (s, 3 H), 4,38 (d, J = 7,8 Hz, 1 H), 6,57 (d, J = 8,6 Hz, 2 H), 7,23 (d, J = 8,6 Hz, 2 H), 7,29 - 7,39 (m, 2 H), 7,49 (s, 1 H), 7,59 (s, 1 H), 7,75 (s, 1 H).

Ejemplo A182

Ácido 3-[{[4-({1-[5-(6-metoxipiridin-3-il)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico



(1) 1-(5-bromo-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ona

La 1-[5-bromo-2-hidroxifenil]etanona (8,4 g) se disolvió en N,N-dimetilformamida (50 mL). A la mezcla de reacción se añadieron carbonato (16,2 g) y 1-bromo-3-metilbutan-2-ona (8,4 g) sintetizada en el Ejemplo A75(1) a temperatura

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ambiente y la mezcla se agitó a 60 °C durante 1 h. La mezcla de reacción se filtró a través de celite, agua (100 mL) se añadió y la mezcla se extrajo con éter dietílico (50 mL×2). El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El precipitado se lavó con éter diisopropílico para dar el compuesto objeto del título (10,2 g, 77%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,25 (d, J = 6,8 Hz, 6 H), 2,57 (s, 3 H), 3,48 - 3,70 (m. 1 H), 7,39 (d, J = 8,7 Hz, 1 H), 7,55 (dd, J = 8,7, 1,9 Hz, 1 H), 7,78 (d, J = 1,9 Hz, 1 H).

(2) 3-{[(4-{[1-(5-bromo-3-metil-1-benzofuran-2-il)-2-metilpropil]amino}fenil)carbonil](metil)amino}propanoato de etilo

1-(5-Bromo-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ona (6,2 g) sintetizada en el punto (1) antes mencionado se disolvió en tetrahidrofurano (100 mL) y metanol (10 mL) y el borohidruro de sodio (90%, 1,8 g) se añadió a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se enfrió con hielo nuevamente y agua (10 mL) y ácido clorhídrico 1 N (50 mL) se añadieron cuidadosamente a la mezcla y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar 1-(5-bromo-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ol (6,1 g, cuantitativo) en forma de un aceite amarillo pálido. El aceite obtenido se disolvió en tetrahidrofurano (50 mL) y

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cloruro de tionilo (2,3 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de hidrógeno-carbonato de sodio (30 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (100 mL), yoduro de sodio (3,9 g), carbonato de sodio (2,7 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (4,4 g) sintetizado en el Ejemplo 2(2) se añadieron a la solución y la mezcla se agitó a 70 °C durante 4 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (1,12 g, 12%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,4 Hz, 3 H), 1,13 (d, J = 6,4 Hz, 3 H), 1,18 - 1,26 (t, J = 7,2 Hz, 3 H), 2,20 - 2,35 (m, 4 H), 2,61 (t, J = 7,0 Hz, 2 H), 3,01 (s, 4 H), 3,70 (t, J = 7,0 Hz, 2 H), 4,09 - 4,17 (m, 2 H), 4,24 - 4,41 (m, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 7,15 - 7,36 (m, 4 H), 7,55 (d, J = 1,9 Hz, 1 H).

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(3) ácido 3-[{[4-({1-[5-(6-metoxipiridin-3-il)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico

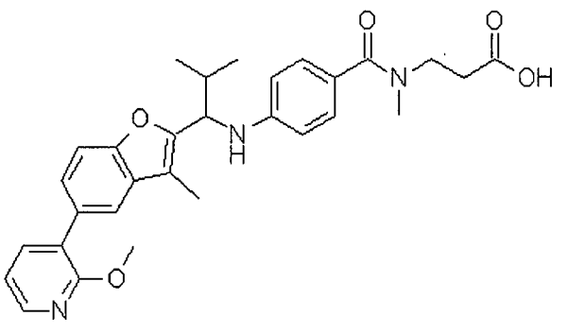
A una solución (10 mL) de 3-{[(4-{[1-(5-bromo-3-metil-1-benzofuran-2-il)-2-metilpropil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,55 g) sintetizado en el punto (2) antes mencionado en N,N-dimetilacetamida se añadieron ácido (6-metoxipiridin-3-il)borónico (0,33 g), carbonato de potasio (0,29 g) y tetrakistrifenilfosfina paladio (0,12 g) y la mezcla se agitó a 70 °C durante 24 h bajo una atmósfera de argón. La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró a través de celite y el residuo se lavó con éter dietílico. Se añadió agua al filtrado y la capa orgánica se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({1-[5-(6-metoxipiridin-3-il)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,10 g) en forma de un aceite amarillo pálido. El aceite obtenido se disolvió en etanol (1 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,06 g, 10%) en forma de un sólido incoloro.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 (d, J = 6,8 Hz, 3 H), 1,15 (d, J = 6,8 Hz, 3 H), 2,15 - 2,37 (m, 1 H), 2,29 (s, 3 H), 2,66 (t, J = 6,2 Hz, 2 H), 3,03 (s, 3 H), 3,70 (t, J = 6,2 Hz, 2 H), 3,98 (s, 3 H), 4,36 (d, J = 7,5 Hz, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 6,82 (d, J = 8,7 Hz, 1 H), 7,23 (d, J = 8,7 Hz, 2 H), 7,30 - 7,46 (m, 2 H), 7,53 (d, J = 1,9 Hz, 1 H), 7,79 (dd, J = 8,5, 2,4 Hz, 1 H), 8,38 (d, J = 2,4 Hz, 1 H).

Ejemplo A183

Ácido 3-[{[4-({1-[5-(2-metoxipiridin-3-il)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico



A una solución (10 mL) de 3-{[(4-{[1-(5-bromo-3-metil-1-benzofuran-2-il)-2-metilpropil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,55 g) sintetizado en el Ejemplo A182(2) en N,N-dimetilacetamida se añadieron ácido (2-metoxipiridin-3-il)borónico (0,33 g), carbonato de potasio (0,29 g) y tetrakistrifenilfosfina paladio (0,12 g) y la mezcla se agitó a 70 °C durante 24 h bajo una atmósfera de argón. La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró a través de celite y el residuo se lavó con éter dietílico.

1655

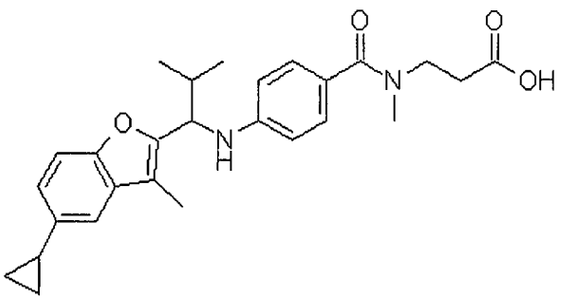
Se añadió agua al filtrado y la capa orgánica se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({1-[5-(2-metoxipiridin-3-il)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,10 g) en forma de un aceite amarillo pálido. El aceite obtenido se disolvió en etanol (1 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida, ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,18 g, 33%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 (d, J = 6,4 Hz, 3 H), 1,15 (d, J = 6,4 Hz, 3 H), 2,12 - 2,40 (m, 1 H), 2,27 (s, 3 H), 2,67 (t, J = 6,2 Hz, 2 H), 3,04 (s, 3 H), 3,70 (t, J = 6,2 Hz, 2 H), 3,96 (s, 3 H), 4,36 (d, J = 7,9 Hz, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 6,97 (dd, J = 7,2, 4,9 Hz, 1 H), 7,23 (d, J = 8,7 Hz, 2 H), 7,33 - 7,77 (m, 4 H), 8,16 (dd, J = 4,9, 1,9 Hz, 1 H).

Ejemplo A184

Ácido 3-{[(4-{[1-(5-ciclopropil-3-metil-1-benzofuran-2-il)-2-metilpropil]amino}fenil)carbonil](metil)amino}propanoico

1686



(1)1-(5-ciclopropil-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ona

A una solución (20 mL) de 1-(5-bromo-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ona (1,0 g) sintetizada en el Ejemplo A182(1) en tolueno se añadieron ácido ciclopropanborónico (0,92 g), solución acuosa 2 N de carbonato de sodio (5,3 mL) y la mezcla se agitó a temperatura ambiente durante 10 min bajo una atmósfera de argón. A la mezcla de reacción se añadieron 2-diciclohexilfosfino-2',6'-dimetoxibifenilo (0,18 g) y tris(dibencilidenacetona)dipaladio (0) (0,10 g) y la mezcla se calentó a reflujo bajo una atmósfera de argón durante la noche. La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró a través de celite y el residuo se lavó con éter dietílico. Se añadió agua al filtrado y la capa orgánica se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:10, relación en volumen) para dar el compuesto objeto del título (0,80 g, 93%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,59 - 1,08 (m, 4 H), 1,23 (d, J = 6,8 Hz, 6 H), 1,91 - 2,11 (m, 1 H), 2,35 (s, 1 H), 2,58 (s, 3 H), 7,07 - 7,51 (m, 3 H).

(2) 1-(5-ciclopropil-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ol

1-(5-Ciclopropil-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ona (0,80 g) sintetizada en el punto (1) antes mencionado se disolvió en tetrahidrofurano (10 mL) y metanol (1 mL) y borohidruro de sodio (90%, 0,34 g) se añadió a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se enfrió con hielo nuevamente y agua (1 mL) y ácido clorhídrico 1 N (5 mL) se añadieron cuidadosamente a la mezcla y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (0,4 g, 50%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,63 - 0,75 (m, 2 H), 0,80 (d, J = 6,8 Hz, 3 H), 0,88 - 1,01 (m, 2 H), 1,11 (d, J = 6,8 Hz, 3 H), 1,20 - 1,30 (m, 1 H), 1,93 - 2,03 (m, 1 H), 2,12 - 2,30 (m, 4 H), 4,46 (d, J = 8,3 Hz, 1 H), 7,01 (dd, J = 8,3, 1,9 Hz, 1 H), 7,17 (d, J = 1,9 Hz, 1 H), 7,29 (d, J = 8,3 Hz, 1 H).

(3) ácido 3-{[(4-{[1-(5-ciclopropil-3-metil-1-benzofuran-2-il)-2-metilpropil]amino}fenil)carbonil](metil)amino}propanoico

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A una solución (5 mL) de 1-(5-ciclopropil-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ol (0,40 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió cloruro de tionilo (0,22 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de carbonato ácido de sodio (5 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (5 mL), se añadieron yoduro de sodio (0,373 g), carbonato de sodio (0,25 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,41 g) sintetizado en el Ejemplo 2(2) a la solución y la mezcla se agitó a 70 °C durante 12 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-{[(4-{[1-(5-ciclopropil-3-metil-1-benzofuran-2-il)-2-metilpropil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,25 g) en forma de un aceite amarillo pálido. El aceite obtenido se disolvió en etanol (2 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a

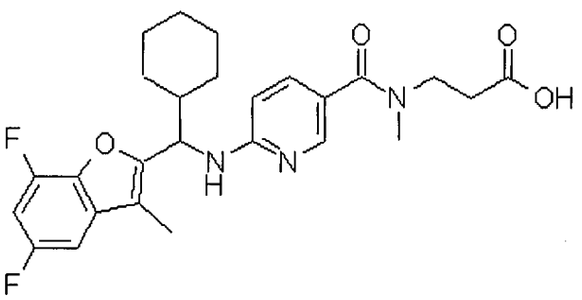
1659

presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,24 g, 32%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,62 - 0,73 (m, 2 H), 0,82 - 1,00 (m, 5 H), 1,12 (d, J = 6,8 Hz, 3 H), 1,90 - 2,07 (m, 1 H), 2,14 - 2,32 (m, 4 H), 2,67 (t, J = 6,2 Hz, 2 H), 3,03 (s, 3 H), 3,70 (t, J = 6,2 Hz, 2 H), 4,32 (d, J = 7,9 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,98 (dd, J = 8,7, 1,9 Hz, 1 H), 7,13 (d, J = 1,9 Hz, 1 H), 7,19 - 7,25 (m, 3 H).

Ejemplo A185

Ácido 3-{[(6-{[ciclohexil(5,7-difluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil](metil)amino}propanoico




El ciclohexil(5,7-difluoro-3-metil-1-benzofuran-2-il)metanol (0,52 g) sintetizado en el Ejemplo A163(2) se disolvió en tetrahidrofurano (5 mL) y el cloruro de tionilo (0,24 mL) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa

de carbonato ácido de sodio (3 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (5 mL), se añadieron yoduro de sodio (0,45 g), carbonato de sodio (0,30 g), etil 6-aminopiridin-3-carboxilato de (0,45 g) a la solución y la mezcla se agitó a 60 °C durante la noche. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con éter dietílico. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 6-{[ciclohexil(5,7-difluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-carboxilato de etilo (0,10 g) en forma de un aceite amarillo. El aceite obtenido se disolvió en tetrahidrofurano (2 mL) y etanol (2 mL) y la mezcla se agitó en presencia de solución acuosa 1 N de hidróxido de sodio (2 mL) at 100 °C durante 12 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y se concentró a presión reducida. El residuo se disolvió en N,N-dimetilformamida (20 mL), 3-(metilamino)propanoato de etilo (0,24 g), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (0,48 g) y monohidrato de hidroxibenzotriazol (0,38 g) se añadieron a la solución y la mezcla se agitó a 70 °C durante 4 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, agua se añadió y la mezcla se extrajo con éter dietílico. El extracto se lavó con

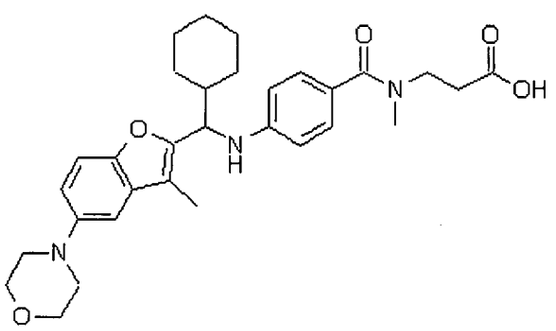
1661

salmuera saturada y se secó sobre sulfato de magnesio. El solvente se evaporó a presión reducida, etanol (5 mL) y solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadieron al residuo y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se concentró a presión reducida, se neutralizó con ácido clorhídrico 1 N (1,0 mL) y se extrajo con acetato de etilo. El extracto se evaporó a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (0,05 g, 6%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,00 - 1,93 (m, 11 H), 2,22 (s, 3 H), 2,68 - 2,75 (m, 2 H), 3,09 (s, 3 H), 3,70 - 3,80 (m, 2 H), 4,10 - 4,20 (m, 1 H), 6,36 (d, J = 8,7 Hz, 1 H), 6,69 - 6,94 (m, 2 H), 7,50 - 7,58 (m, 1 H), 8,15 (d, J = 1,9 Hz, 1 H).

Ejemplo A186

Ácido 3-[{[4-({ciclohexil[3-metil-5-(morfolin-4-il)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico



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(1) 5-bromo-3-metil-1-benzofuran-2-carboxilato de metilo

A una solución (200 mL) de 1-(5-bromo-2-hidroxifenil)etanona (25,0 g) en N,N-dimetilformamida se añadieron carbonato de potasio (24,0 g) y bromoacetato de metilo (11,5 mL) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se filtró, el 1,8-diazabiciclo[5,4,0]undec-7-eno (23,2 mL) se añadió al filtrado y la mezcla se agitó a 100 °C durante 3 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y se añadió agua helada. El precipitado se lavó con etanol-agua para dar el compuesto objeto del título (16,8 g, 52%) en forma de un sólido de color rojo pálido.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,56 (s, 3 H), 3,99 (s, 3 H), 7,36 - 7,46 (m, 1 H), 7,49 - 7,60 (m, 1 H), 7,77 (d, J = 2,3 Hz, 1 H).

(2) 3-metil-5-(morfolin-4-il)-1-benzofuran-2-carboxilato de metilo

A una solución (100 mL) de 5-bromo-3-metil-1-benzofuran-2-carboxilato de metilo (5,4 g) sintetizada en el punto (1) antes mencionado en tolueno se añadieron morfolina (5,2 mL), carbonato de cesio (13,0 g), tris(dibencilidenacetona)dipaladio (0) (0,92 g) y 9,9-dimetil-4,5-bis(difenilfosfino)xanteno (1,1 g) y la mezcla se calentó a reflujo bajo una atmósfera de argón durante 20 h. La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró a través de celite. Se añadió agua al residuo y la

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mezcla se extrajo con acetato de etilo. El extracto se concentró y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (0,69 g, 13%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,57 (s, 3 H), 3,06 - 3,22 (m, 4 H), 3,83 - 3,94 (m, 4 H), 3,97 (s, 3 H), 7,02 (d, J = 2,3 Hz, 1 H), 7,15 (dd, J = 9,0, 2,3 Hz, 1 H), 7,45 (d, J = 9,0 Hz, 1 H).

(3) 3-metil-5-(morfolin-4-il)-1-benzofuran-2-carbaldehído

Una solución (2 mL) de 3-metil-5-(morfolin-4-il)-1-benzofuran-2-carboxilato de metilo (0,69 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió a una solución helada (5 mL) de hidruro de litio y aluminio (0,25 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se enfrió con hielo nuevamente y agua (0,65 mL), solución acuosa 1 N de hidróxido de sodio (3,2 mL) y agua (0,65 mL) se añadieron sucesivamente gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar un producto crudo (0,48 g) de [3-metil-5-(morfolin-4-il)-1-benzofuran-2-il]metanol en forma de un aceite amarillo pálido. El aceite obtenido se disolvió en acetonitrilo (5 mL), perrutenato de tetrapropilamonio (0,07 g) y N-óxido de N-metilmorfolina (0,46 g) se añadieron a la solución a temperatura ambiente y la mezcla se agitó durante 30 min. El solvente se evaporó a presión reducida y el residuo se

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purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (0,24 g, 40%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,59 (s, 3 H), 3,09 - 3,22 (m, 4 H), 3,79 - 3,98 (m, 4 H), 7,05 (d, J = 2,3 Hz, 1 H), 7,23 (dd, J = 9,2, 2,3 Hz, 1 H), 7,46 (d, J = 9,2 Hz, 1 H), 10,00 (s, 1 H).

(4) ciclohexil[3-metil-5-(morfolin-4-il)-1-benzofuran-2-il]metanol

A una solución (5 mL) de 3-metil-5-(morfolin-4-il)-1-benzofuran-2-carbaldehído (0,24 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió gota a gota bromuro de ciclohexilmagnesio (2 mL, solución 1 M de tetrahidrofurano) bajo enfriamiento con hielo. Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar ciclohexil[3-metil-5-(morfolin-4-il)-1-benzofuran-2-il]metanol (0,39 g, cuantitativo) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,07 - 2,01 (m, 12 H), 2,19 (s, 3 H), 3,11 - 3,21 (m, 4 H), 3,83 - 3,95 (m, 4 H), 4,50 (d, J

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= 8,7 Hz, 1 H), 6,90 - 7,01 (m, 2 H), 7,33 (d, J = 9,8 Hz, 1 H).

(5) ácido 3-[{[4-({ciclohexil[3-metil-5-(morfolin-4-il)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (5 mL) de ciclohexil[3-metil-5-(morfolin-4-il)-1-benzofuran-2-il]metanol (0,39 g) sintetizada en el punto (4) antes mencionado en tetrahidrofurano se añadió cloruro de tionilo (0,13 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y se añadió cuidadosamente una solución saturada acuosa de carbonato ácido de sodio (5 mL). La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (5 mL), yoduro de sodio (0,23 g), carbonato de sodio (0,15 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,25 g) sintetizado en el Ejemplo 2(2) se añadieron a la solución y la mezcla se agitó a 70 °C durante 15 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[3-metil-5-(morfolin-4-il)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de

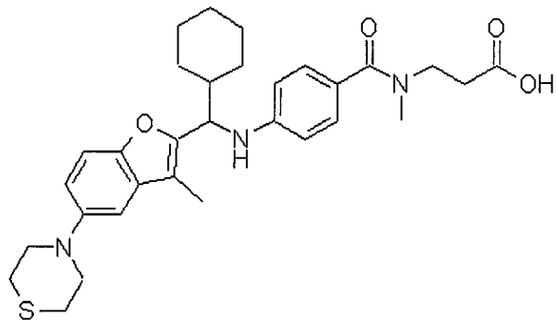
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etilo (0,25 g) en forma de un aceite amarillo pálido. El aceite obtenido se disolvió en etanol (2 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,19 g, 33%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 2,16 (m, 11 H), 2,22 (s, 3 H), 2,68 (br. s., 2 H), 3,04 (s, 3 H), 3,14 (br. s., 4 H), 3,58 - 3,77 (m, 2 H), 3,89 (br. s., 4 H), 4,36 (d, J = 8,3 Hz, 1 H), 6,56 (d, J = 9,0 Hz, 2 H), 6,84 - 7,02 (m, 2 H), 7,17 - 7,27 (m, 3 H).

Ejemplo A187

Ácido 3-[{[4-({ciclohexil[3-metil-5-(tiomorfolin-4-il)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico




(1) ciclohexil[3-metil-5-(tiomorfolin-4-il)-1-benzofuran-2-il]metanona

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A una solución (15 mL) de (5-bromo-3-metil-1-benzofuran-2-il)(ciclohexil)metanona (0,75 g) sintetizado en el Ejemplo A174(1) en tolueno se añadieron tiomorfolina (0,72 g), carbonato de cesio (2,3 g), tris(dibencilidenacetona)dipaladio (0) (0,16 g) y 9,9-dimetil-4,5-bis(difenilfosfino)xanteno (0,2 g) y la mezcla se calentó a reflujo bajo una atmósfera de argón durante 18 h. La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró a través de celite, se añadió agua al residuo y la mezcla se extrajo con acetato de etilo. El extracto se concentró para dar un producto crudo (0,83 g, cuantitativo) del compuesto objeto del título en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,37 - 2,01 (m, 10 H), 2,56 (s, 3 H), 2,70 - 2,88 (m, 4 H), 3,25 - 3,40 (m, 1 H), 3,42 - 3,70 (m, 4 H), 7,00 - 7,78 (m, 3 H).

(2) ciclohexil[3-metil-5-(tiomorfolin-4-il)-1-benzofuran-2-il]metanol

La ciclohexil[3-metil-5-(tiomorfolin-4-il)-1-benzofuran-2-il]metanona (0,83 g) sintetizada en el punto (1) antes mencionado se disolvió en tetrahidrofurano (10 mL) y metanol (1 mL) y el borohidruro de sodio (90%, 0,2 g) se añadió a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se enfrió con hielo nuevamente y agua (1 mL) y ácido clorhídrico 1 N (5 mL) se añadieron cuidadosamente y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre

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sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (0,18 g, 22%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,81 - 1,93 (m, 11 H), 2,20 (s, 3 H), 2,70 - 2,91 (m, 4 H), 3,34 - 3,53 (m, 4 H), 4,50 (d, J = 8,3 Hz, 1 H), 4,99 (t, J = 6,4 Hz, 1 H), 6,90 - 7,40 (m, 3 H).

(3) ácido 3-[{[4-({ciclohexil[3-metil-5-(tiomorfolin-4-il)-1-benzofuran-2-
il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución (5 mL) de ciclohexil[3-metil-5-(tiomorfolin-4-il)-1-benzofuran-2-il]metanol (0,18 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió cloruro de tionilo (0,07 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de hidrógeno-carbonato de sodio (5 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (5 mL), se añadieron yoduro de sodio (0,15 g), carbonato de sodio (0,10 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,13 g) sintetizado en el Ejemplo 2(2) a la solución y la mezcla se

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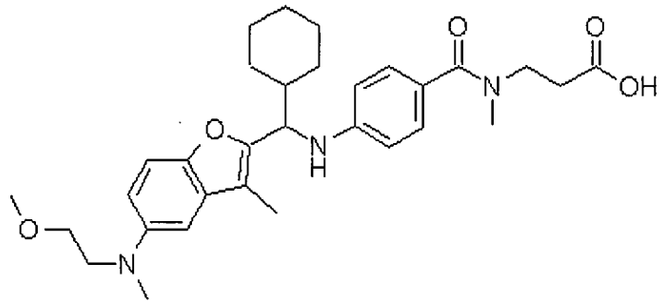
agitó a 70 °C durante 15 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[{[4-({ciclohexil[3-metil-5-(tiomorfolin-4-il)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (0,08 g) en forma de un aceite amarillo pálido. El aceite obtenido se disolvió en etanol (2 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,05 g, 18%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,88 - 2,17 (m, 11 H), 2,20 (s, 3 H), 2,59 (br. s., 2 H), 2,80 - 3,20 (m, 7 H), 3,50 - 3,70 (m, 6 H), 4,38 (d, J = 7,9 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 7,08 - 7,47 (m, 5 H).

Ejemplo A188

Ácido 3-[({4-[(ciclohexil{5-[(2-metoxietil)(metil)amino]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

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(1) 5-[(2-metoxietil)(metil)amino]-3-metil-1-benzofuran-2-carboxilato de metilo

A una solución (50 mL) de 5-bromo-3-metil-1-benzofuran-2-carboxilato de metilo (2,7 g) sintetizado en el Ejemplo A186(1) en tolueno se añadieron 2-metoxi-N-metiletanamina (2,7 g), carbonato de cesio (9,8 g), tris(dibencilidenacetona)dipaladio (0) (0,69 g) y 9,9-dimetil-4,5-bis(difenilfosfino)xanteno (0,87 g) y la mezcla se calentó a reflujo bajo una atmósfera de argón durante 6 h. La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró a través de celite, se añadió agua al filtrado y la mezcla se extrajo con acetato de etilo. El extracto se concentró y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:4, relación en volumen) para dar el compuesto objeto del título (2,7 g, cuantitativo) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,55 (s, 3 H), 3,01 (s, 3 H), 3,37 (s, 3 H), 3,40 - 3,70 (m, 4 H), 3,97 (s, 3 H), 6,77 - 7,15 (m, 3 H).

(2) 5-[(2-metoxietil)(metil)amino]-3-metil-1-benzofuran-2-carbaldehído

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Una solución (10 mL) de 5-[(2-metoxietil)(metil)amino]-3-metil-1-benzofuran-2-carboxilato de metilo (2,7 g) sintetizada en el punto (1) antes mencionado en tetrahidrofurano se añadió a una solución helada (40 mL) de hidruro de litio y aluminio (0,38 g) en tetrahidrofurano. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se enfrió con hielo nuevamente y se añadieron sucesivamente agua (1,0 mL), solución acuosa 1 N de hidróxido de sodio (5,0 mL) y agua (1,0 mL) gota a gota para neutralizar la reacción. El residuo se filtró a través de celite y el filtrado se concentró a presión reducida para dar un producto crudo (0,41 g) de {5-[(2-metoxietil)(metil)amino]-3-metil-1-benzofuran-2-il}metanol en forma de un aceite amarillo pálido. El aceite obtenido se disolvió en acetonitrilo (20 mL), perrutenato de tetrapropilamonio (0,07 g) y N-óxido de N-metilmorfolina (0,46 g) se añadieron a la solución a temperatura ambiente y la mezcla se agitó durante 30 min. El solvente se evaporó a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (0,09 g, 3%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,58 (s, 3 H), 3,02 (s, 3 H), 3,38 (s, 3 H), 3,47 - 3,66 (m, 4 H), 6,81 (d, J = 2,6 Hz, 1 H), 7,10 (dd, J = 9,0, 2,6 Hz, 1 H), 7,40 (d, J = 9,0 Hz, 1 H), 9,97 (s, 1 H).

(3) ciclohexil{5-[(2-metoxietil)(metil)amino]-3-metil-1-benzofuran-2-il}metanol

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A una solución (5 mL) de 5-[(2-metoxietil)(metil)amino]-3-metil-1-benzofuran-2-carbaldehído (0,09 g) sintetizado en el punto (2) antes mencionado en tetrahidrofurano se añadió gota a gota bromuro de ciclohexilmagnesio (2 mL, solución 1 M de tetrahidrofurano) bajo enfriamiento con hielo. Después de completar la adición gota a gota, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 15 min. A la mezcla de reacción se añadió solución acuosa de cloruro de amonio y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:2, relación en volumen) para dar el compuesto objeto del título (0,11 g, cuantitativo) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,99 - 1,96 (m, 12 H), 2,18 (s, 3 H), 2,99 (s, 3 H), 3,37 (s, 3 H), 3,45 - 3,72 (m, 4 H), 4,49 (d, J = 8,7 Hz, 1 H), 6,77 - 7,30 (m, 3 H).

(4) ácido 3-[({4-[(ciclohexil{5-[(2-metoxietil)(metil)amino]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

A una solución (10 mL) de ciclohexil{5-[(2-metoxietil)(metil)amino]-3-metil-1-benzofuran-2-il}metanol (0,11 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió cloruro de tionilo (0,10 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y una solución saturada acuosa de hidrógeno-carbonato de sodio (5 mL) se añadió cuidadosamente a la mezcla. La

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mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se disolvió en dimetilacetamida (10 mL), se añadieron yoduro de sodio (0,14 g), carbonato de sodio (0,09 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,15 g) sintetizado en el Ejemplo 2(2) a la solución y la mezcla se agitó a 70 °C durante 4 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar 3-[({4-[(ciclohexil{5-[(2-metoxietil)(metil)amino]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoato de etilo (0,03 g) en forma de un aceite amarillo pálido. El aceite obtenido se disolvió en etanol (2 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el compuesto objeto del título (0,02 g, 11%) en forma de un sólido incoloro.

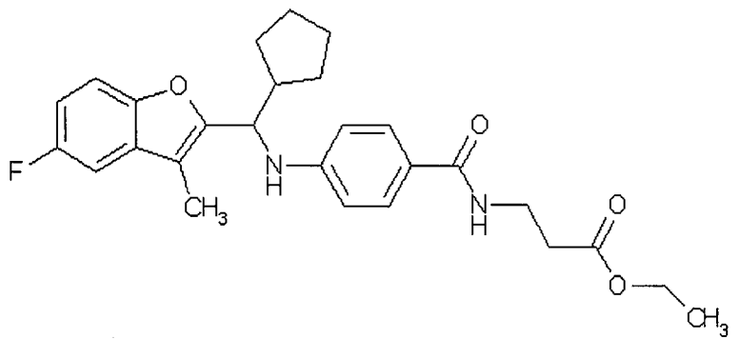
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,90 - 2,13 (m, 11 H), 2,21 (s, 3 H), 2,68 (br. s., 2 H), 2,98 (s, 3 H), 3,05 (s, 3 H), 3,36 (s, 3 H), 3,41 - 3,62 (m, 4 H), 3,68 (br. s., 2 H), 4,35 (d,

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J = 8,0 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,67 - 6,88 (m, 2 H), 7,13 - 7,25 (m, 3 H).

Ejemplo A189

3-{[(4-{[ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo



(1) 4-{[(E)-ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metiliden]amino}benzoato de metilo

A una mezcla de ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metanona (1,3 g) sintetizada en el Ejemplo A67(3), 4-aminobenzoato de metilo (798 mg), trietilamina (5,88 mL) y diclorometano (13 mL) se añadió cloruro de titanio (IV) (solución 1,0 M de diclorometano, 6,3 mL) a 0 °C y la mezcla se agitó a temperatura ambiente durante 2 h bajo una atmósfera de nitrógeno. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción. El solvente se concentró a presión reducida y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un sólido marrón oscuro. A una solución del sólido obtenido en

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tetrahidrofurano (20 mL) se añadieron cianoborohidruro de sodio (657 mg) y ácido acético (1,50 mL) y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió solución saturada acuosa de carbonato ácido de sodio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 90:10) para dar el compuesto del título (1,27 g, 63%) en forma de un compuesto amorfo amarillo. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,49 - 1,69 (m, 8 H), 2,26 (s, 3 H), 2,43 - 2,56 (m, 1 H), 3,82 (s, 3 H), 4,34 - 4,45 (m, 1 H), 4,55 (d, J = 8,3 Hz, 1 H), 6,56 (d, J = 9,0 Hz, 2 H), 6,86 - 6,98 (m, 1 H), 7,02 - 7,14 (m, 1 H), 7,23 - 7,35 (m, 1 H), 7,79 (d, J = 9,0 Hz, 2 H).

(2) ácido 4-{[(E)-ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metiliden]amino}benzoico

A una mezcla de 4-{[(E)-ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metiliden]amino}benzoato de metilo (1,19 g) sintetizado con anterioridad, tetrahidrofurano (6 mL) y etanol (6 mL) se añadió solución acuosa 1 N de hidróxido de sodio (6 mL) y la mezcla se agitó con calentamiento a reflujo durante 3,5 h. Adicionalmente se agregó solución acuosa 1 N de hidróxido de sodio (6 mL) a la mezcla y la mezcla se agitó con calentamiento a reflujo durante 14 h. La mezcla de reacción se concentró a presión reducida, ácido clorhídrico 1 N (11 mL) se añadió al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada,

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se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto del título (1,08 g, 94%) como una forma amorfa incolora.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,39 - 1,76 (m, 8 H), 1,89 - 1,99 (m, 1 H), 2,24 (s, 3 H), 2,40 - 2,55 (m, 1 H), 4,40 (d, J = 9,1 Hz, 1 H), 6,52 (d, J = 8,7 Hz, 2 H), 6,82 - 6,98 (m, 1 H), 7,02 - 7,13 (m, 1 H), 7,03 - 7,11 (m, 1 H), 7,22 - 7,29 (m, 1 H), 7,81 (d, J = 8,7 Hz, 2 H).

(3) 3-{[(4-{[ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo

Una solución de ácido 4-{[(E)-ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metiliden]amino}benzoico (483 mg) sintetizado con anterioridad, clorhidrato de éster etílico de β-alanina (241 mg), monohidrato de 1-hidroxibenzotriazol (240 mg), trietilamina (438 µL) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (301 mg) en N,N-dimetilformamida (10 mL) se agitó a temperatura ambiente durante 3 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 60:40, v/v) para dar el compuesto del título (397 mg, 65%) como una forma amorfa incolora.

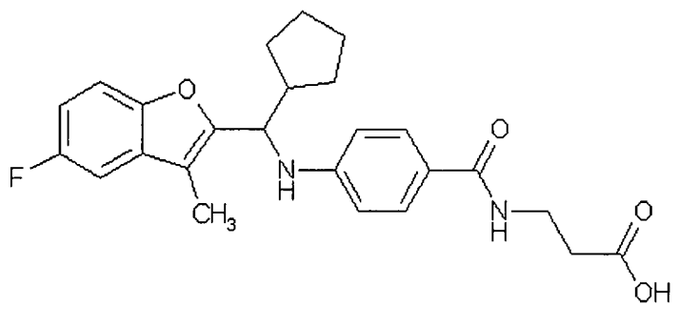
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,21 - 1,31 (m, 3 H), 1,50 - 1,70 (m, 8 H), 1,92 - 2,01 (m, 1 H), 2,25 (s, 3 H), 2,42 - 2,55 (m, 1 H), 2,58 (t, J = 5,9 Hz, 2 H), 3,65 (q, J = 6,1

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Hz, 2 H), 4,31 - 4,49 (m, 2 H), 6,57 (d, J = 8,7 Hz, 3 H), 6,84 - 6,98 (m, 1 H), 7,06 (dd, J = 8,3, 2,7 Hz, 1 H), 7,21 - 7,32 (m, 1 H), 7,54 (d, J = 8,7 Hz, 2 H).

Ejemplo A190

Ácido 3-{[(4-{[ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoico



El 3-{[(4-{[ciclopentil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil]amino}propanoato de etilo (363 mg) sintetizado en el Ejemplo A189 se disolvió en etanol (1,5 mL) y tetrahidrofurano (1,5 mL), una solución acuosa 1 N de hidróxido de sodio (1,5 mL) se añadió a la solución y la mezcla se agitó a temperatura ambiente durante 30 min. El solvente se evaporó a presión reducida, se añadió agua (4 mL) a la mezcla y la mezcla se neutralizó con ácido clorhídrico 1 N bajo enfriamiento con hielo y la mezcla se agitó durante 30 min. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (283 mg, 83%) en forma de un sólido incoloro.

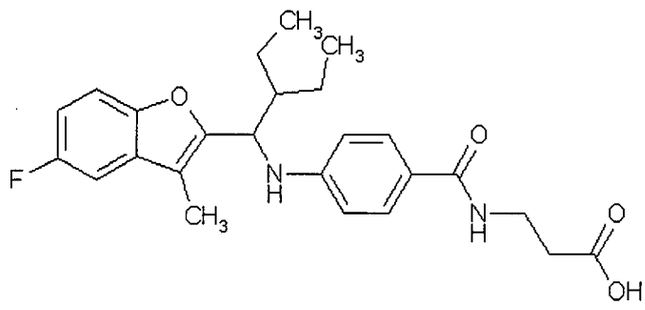
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,21 - 1,72 (m, 7 H), 1,91 - 2,04 (m, 1 H), 2,24 (s, 3 H), 2,47 (q, J = 8,1 Hz, 1 H), 2,62 (t, J = 5,9 Hz, 2 H), 3,63 (q, J = 6,1 Hz, 2 H), 4,38 (d, J =

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9,1 Hz, 1 H), 6,51 - 6,64 (m, 3 H), 6,86 - 6,97 (m, 1 H), 7,06 (dd, J = 8,5, 2,5 Hz, 1 H), 7,19 - 7,32 (m, 2 H), 7,52 (d, J = 8,7 Hz, 2 H).

Ejemplo A191

Ácido 3-{[(4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butil]amino}fenil)carbonil]amino}propanoico



Una solución de ácido 4-{[2-etil-1-(5-fluoro-3-metil-1-benzofuran-2-il)butil]amino}benzoico (180 mg) sintetizado en el Ejemplo A71(4), clorhidrato de éster etílico de β-alanina (89 mg), monohidrato de 1-hidroxibenzotriazol (89 mg), trietilamina (163 µL) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (111 mg) en N,N-dimetilformamida (5 mL) se agitó a temperatura ambiente durante 6 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 60:40, v/v) para dar un aceite incoloro (159 mg). El aceite incoloro obtenido (159 mg) se disolvió en

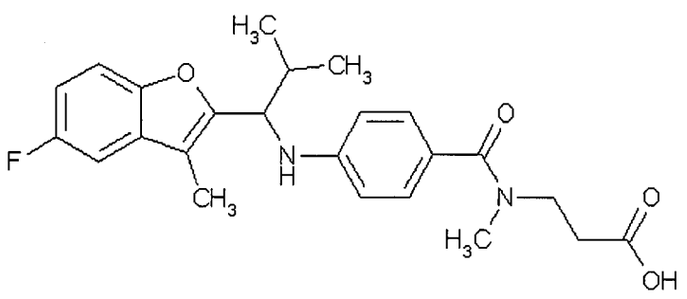
1679

etanol (1,0 mL) y tetrahidrofurano (1,0 mL), solución acuosa 1 N de hidróxido de sodio (0,66 mL) se añadió a la solución y la mezcla se agitó a temperatura ambiente durante 1 h. El solvente se evaporó a presión reducida, se añadió agua (4 mL), se neutralizó con ácido clorhídrico 1 N bajo enfriamiento con hielo y la mezcla se agitó durante 30 min. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (87 mg, 41%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 (t, J = 7,4 Hz, 3 H), 0,94 (t, J = 7,6 Hz, 3 H), 1,14 - 1,68 (m, 4 H), 1,80 - 1,92 (m, 1 H), 2,21 (s, 3 H), 2,63 (t, J = 5,7 Hz, 2 H), 3,64 (q, J = 6,1 Hz, 2 H), 4,58 (d, J = 7,6 Hz, 1 H), 6,49 - 6,64 (m, 3 H), 6,92 (td, J = 9,1, 2,7 Hz, 1 H), 7,05 (dd, J = 8,5, 2,5 Hz, 1 H), 7,22 - 7,29 (m, 1 H), 7,53 (d, J = 8,7 Hz, 2 H).

Ejemplo A192

Ácido 3-{[(4-{[1-(5-fluoro-3-metil-1-benzofuran-2-il)-2-metilpropil]amino}fenil)carbonil](metil)amino}propanoico




(1)1-(5-fluoro-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ona

A una solución de 5-fluoro-3-metil-1-benzofurano (2,0 g) sintetizada en el Ejemplo A67(2) y cloruro de isobutirilo

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(1,56 g) en nitrometano (40 mL) se añadió cloruro de aluminio (anhidro) (2,66 g) a 0 °C y la mezcla se agitó a 0 °C durante 1 h y a temperatura ambiente durante 12 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 90:10, v/v) para dar el compuesto del título (1,933 g, 66%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,24 (d, J = 7,2 Hz, 6 H), 2,57 (s, 3 H), 3,44 - 3,65 (m, 1 H), 7,11 - 7,33 (m, 2 H), 7,41 - 7,50 (m, 1 H)

(2) 1-(5-fluoro-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ol

La 1-(5-fluoro-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ona (11,66 g) sintetizada con anterioridad se disolvió en metanol (4 mL)-tetrahidrofurano (20 mL) y tetraborohidrato de sodio (90%)(446 mg) se añadió a la solución a 0 °C. La mezcla de reacción se agitó a 0 °C durante 1 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar el compuesto del título (1,193 g, 100%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,82 (d, J = 6,8 Hz, 3 H), 1,12 (d, J = 6,8 Hz, 3 H), 1,99 - 2,06 (m, 1 H), 2,15 - 2,27 (m, 4 H), 4,43 - 4,52 (m, 1 H), 6,91 - 7,01 (m, 1 H), 7,11 (dd, J = 8,7, 2,6 Hz, 1 H), 7,33 (dd, 1 H).

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(3) ácido 3-{[(4-{[1-(5-fluoro-3-metil-1-benzofuran-2-il)-2-metilpropil]amino}fenil)carbonil](metil)amino}propanoico

A una solución de 1-(5-fluoro-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ol (1,128 g) obtenida con anterioridad en tetrahidrofurano (10 mL) se añadió cloruro de tionilo (0,45 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 2 h. A la mezcla de reacción se añadió solución acuosa de carbonato ácido de sodio y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar 2-(1-cloro-2-metilpropil)-5-fluoro-3-metil-1-benzofurano crudo (1,10 g). Al 2-(1-cloro-2-metilpropil)-5-fluoro-3-metil-1-benzofurano obtenido (500 mg) se añadieron 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (546 mg) obtenido en el Ejemplo 2 (2), yoduro de sodio (623 mg), carbonato de sodio (441 mg) y N,N-dimetilformamida (5 mL) y la mezcla se agitó a 80 °C durante 13 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 50:50, v/v) para dar un compuesot amorfo amarillo (287 mg). El compuesto amorfo obtenido (280 mg) se disolvió en etanol (2,4 mL) y tetrahidrofurano (2,4 mL) y una solución acuosa 1 N de hidróxido de sodio (1,2 mL) se añadió

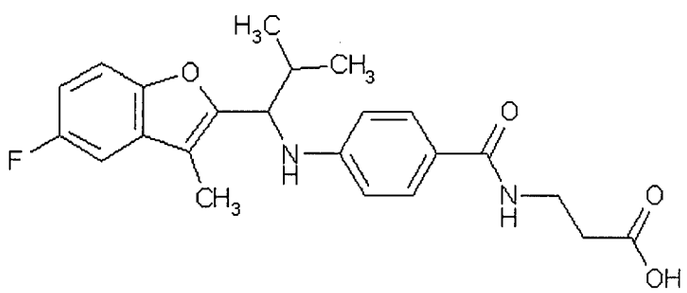
1682

a la solución y la mezcla se agitó a temperatura ambiente durante 1,5 h. El solvente se evaporó a presión reducida, se añadió agua (4 mL), la mezcla se neutralizó con ácido clorhídrico 1 N (1,2 mL) bajo enfriamiento con hielo y la mezcla se agitó durante 1,5 h. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (231 mg, 23%) en forma de un compuesto amorfo amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, 3 H), 1,13 (d, J = 6,4 Hz, 3 H), 2,18 - 2,30 (m, 4 H), 2,66 (t, J = 6,4 Hz, 2 H), 3,03 (s, 3 H), 3,70 (t, J = 6,6 Hz, 2 H), 4,33 (d, J = 7,5 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,93 (td, J = 9,0, 2,6 Hz, 1 H), 7,07 (dd, J = 8,7, 2,6 Hz, 1 H), 7,22 - 7,32 (m, 3 H).

Ejemplo A193

Ácido 3-{[(4-{[1-(5-fluoro-3-metil-1-benzofuran-2-il)-2-metilpropil]amino}fenil)carbonil]amino}propanoico




A una solución de 1-(5-fluoro-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ol (1,128 g) obtenido en el Ejemplo A192(2) en tetrahidrofurano (10 mL) se añadió cloruro de tionilo (0,45 mL) a temperatura ambiente. La mezcla de

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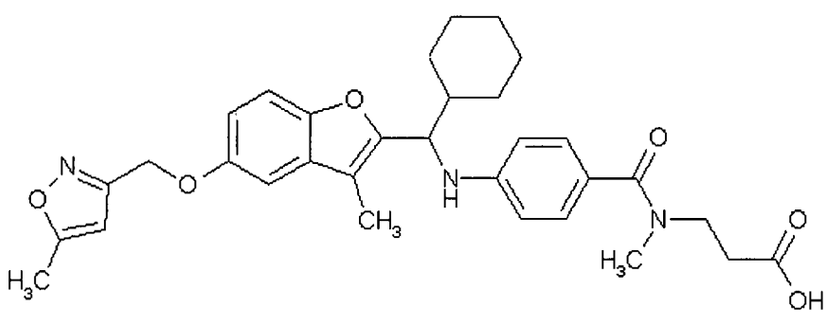
reacción se agitó a temperatura ambiente durante 2 h. A la mezcla de reacción se añadió solución acuosa de hidrógeno-carbonato de sodio y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar 2-(1-cloro-2-metilpropil)-5-fluoro-3-metil-1-benzofurano crudo (1,10 g). Al 2-(1-cloro-2-metilpropil)-5-fluoro-3-metil-1-benzofurano obtenido (485 mg) se añadieron 3-{[(4-aminofenil)carbonil]amino}propanoato de etilo (500 mg) obtenido en el Ejemplo 1(2), yoduro de sodio (599 mg), carbonato de sodio (424 mg) y N,N-dimetilformamida (5 mL) y la mezcla se agitó a 80 °C durante 13 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 50:50, v/v) para dar un compuesto amorfo incoloro (123 mg). El compuesto amorfo obtenido (123 mg) se disolvió en etanol (2,0 mL) y tetrahidrofurano (2,0 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución y la mezcla se agitó a temperatura ambiente durante 1 h. El solvente se evaporó a presión reducida, el se añadió agua (4 mL) al residuo y la mezcla se neutralizó con ácido clorhídrico 1 N (1,0 mL) bajo enfriamiento con hielo y la mezcla se agitó durante 20 min. El precipitado resultante se

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recogió por filtración y se secó para dar el compuesto del título (97 mg, 11%) en forma de un compuesto amorfo amarillo. $^1$H RMN (300 MHz, CLOROFORMO-d) δppm 0,91 (d, 3 H), 1,13 (d, J = 6,8 Hz, 3 H), 2,18 - 2,29 (m, 4 H), 2,64 (t, J = 5,7 Hz, 2 H), 3,65 (q, J = 6,0 Hz, 2 H), 4,35 (d, J = 7,9 Hz, 1 H), 6,57 (d, J = 8,7 Hz, 3 H), 6,92 (td, J = 9,0, 2,6 Hz, 1 H), 7,06 (dd, J = 8,5, 2,4 Hz, 1 H), 7,23 - 7,30 (m, 1 H), 7,54 (d, J = 8,7 Hz, 2 H).

Ejemplo A194

Ácido 3-[({4-[(ciclohexil{3-metil-5-[(5-metilisoxazol-3-il)metoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



(1) [5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metanol

La [5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metanona (23,4 g) sintetizada en el Ejemplo A82(2) se disolvió en metanol (40 mL)-tetrahidrofurano (400 mL) y tetraborohidrato de sodio (90%)(5,64 g) se añadió a la solución a 0 °C. La mezcla de reacción se agitó a 0 °C durante 1 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se

lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar el compuesto del título (25,17 g, 100%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,88 - 1,40 (m, 7 H), 1,61 - 1,70 (m, 2 H), 1,75 - 1,92 (m, 2 H), 1,95 - 1,99 (m, 1 H), 2,18 (s, 3 H), 4,45 - 4,54 (m, 1 H), 5,10 (s, 2 H), 6,94 (dd, J = 9,0, 2,6 Hz, 1 H), 7,00 (d, J = 2,3 Hz, 1 H), 7,28 - 7,49 (m, 6 H).

(2) 5-(benciloxi)-2-[cloro(ciclohexil)metil]-3-metil-1-benzofurano

A una solución de [5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metanol (25,17 g) sintetizado con anterioridad en tetrahidrofurano (250 mL) se añadió cloruro de tionilo (9,44 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 1 h. A la mezcla de reacción se añadió solución acuosa de carbonato ácido de sodio enfriada a 0 °C y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar el compuesto del título (25,39 g, 96%) en forma de un sólido amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,87 - 1,52 (m, 6 H), 1,58 - 1,71 (m, 4 H), 2,19 (s, 3 H), 2,29 - 2,38 (m, 1 H), 4,80 (d, 1 H), 5,10 (s, 2 H), 6,94 - 7,02 (m, 2 H), 7,32 - 7,56 (m, 6 H).

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(3) 3-[{[4-({[5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo

A 5-(benciloxi)-2-[cloro(ciclohexil)metil]-3-metil-1-benzofurano (8,48 g) obtenido con anterioridad se añadieron 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (12,5 g) obtenido en el Ejemplo 2(2), yoduro de sodio (7,62 g), carbonato de sodio (5,39 mg) y N,N-dimetilacetamida (125 mL) y la mezcla se agitó a 60 °C durante 14 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 50:50, v/v) para dar el compuesto del título (14,20 g, 72%) en forma de un compuesto amorfo amarillo.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,88 - 1,26 (m, 5 H), 1,50 - 2,09 (m, 7 H), 2,21 (s, 3 H), 2,56 - 2,73 (m, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,0 Hz, 2 H), 4,06 - 4,18 (m, 2 H), 4,32 - 4,42 (m, 2 H), 4,32 - 4,39 (m, 2 H), 5,08 (s, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,86 - 6,92 (m, 1 H), 6,97 (d, J = 2,3 Hz, 1 H), 7,17 - 7,53 (m, 8 H).

(4) 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

El 3-[{[4-({[5-(benciloxi)-3-metil-1-benzofuran-2-il](ciclohexil)metil}amino)fenil]carbonil}(metil)amino]propanoato de etilo (10,11 g) obtenido con anterioridad se disolvió

1687

en etanol (200 mL) y carbono de paladio al 10% (con agua) (1,0 g) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó bajo una atmósfera de hidrógeno (1 atm) a temperatura ambiente durante 24 h y el catalizador se filtró. El filtrado se concentró a presión reducida para dar el compuesto del título (8,98 g, 100%) en forma de un compuesto amorfo marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,16 (m, 3 H), 1,22 - 1,27 (m, 5 H), 1,52 (d, J = 12,5 Hz, 1 H), 1,65 - 1,95 (m, 4 H), 2,08 - 2,13 (m, 1 H), 2,15 (s, 3 H), 2,62 (t, J = 6,8 Hz, 2 H), 3,02 (s, 3 H), 3,72 (t, J = 7,0 Hz, 2 H), 4,05 - 4,17 (m, 2 H), 4,30 - 4,38 (m, 2 H), 5,58 (s, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,70 (dd, J = 8,5, 2,5 Hz, 1 H), 6,80 (d, J = 2,7 Hz, 1 H), 7,17 (d, J = 8,7 Hz, 1 H), 7,22 (d, J = 8,3 Hz, 2 H).

(5) ácido 3-[({4-[(ciclohexil{3-metil-5-[(5-metilisoxazol-3-il)metoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

Una solución de 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (300 mg) obtenido con anterioridad, (5-metilisoxazol-3-il)metanol (83 mg) y tributilfosfina (308 mg) en tetrahidrofurano (30 mL) se enfrió hasta 0 °C en un baño de hielo y la 1,1'-(azodicarbonil)dipiperidina (308 mg) se añadió a la solución. La mezcla de reacción se agitó a temperatura ambiente durante 3,5 h. Luego se añadieron (5-metilisoxazol-3-il)metanol (83 mg), tributilfosfina (154 mg)

1688

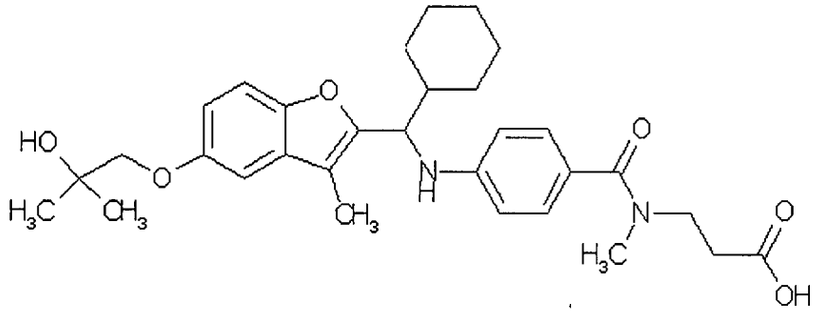
y 1,1'-(azodicarbonil)dipiperidina (154 mg) a la mezcla y la mezcla se agitó a temperatura ambiente durante 14 h. A la mezcla de reacción se añadió hexano (60 mL). El material insoluble se filtró y el filtrado se concentró a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 50:50, v/v) para dar un compuesto amorfo incoloro (105 mg). El compuesto amorfo incoloro obtenido (105 mg) se disolvió en etanol (0,5 mL) y tetrahidrofurano (0,5 mL), una solución acuosa 1 N de hidróxido de sodio (0,36 mL) se añadió a la solución y la mezcla se agitó a temperatura ambiente durante 30 min. El solvente se evaporó a presión reducida, agua (2 mL) se añadió al residuo y la mezcla se neutralizó con ácido clorhídrico 1 N (0,36 mL) bajo enfriamiento con hielo. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (72 mg, 21%) como una forma amorfa incolora.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,01 - 1,25 (m, 5 H), 1,42 - 1,83 (m, 6 H), 2,07 (br. s., 1 H), 2,21 (s, 3 H), 2,41 (s, 3 H), 2,61 - 2,69 (m, 2 H), 3,02 (s, 3 H), 3,68 (t, J = 6,4 Hz, 2 H), 4,35 (d, J = 7,9 Hz, 1 H), 5,13 (s, 2 H), 6,11 (s, 1 H), 6,55 (d, J = 8,3 Hz, 2 H), 6,87 (dd, J = 8,9, 2,4 Hz, 1 H), 6,97 (d, J = 2,6 Hz, 1 H), 7,19 - 7,26 (m, 3 H).

Ejemplo A195

Ácido 3-[{[4-({ciclohexil[5-(2-hidroxi-2-metilpropoxi)-3-metil-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

1689



Una solución de 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (300 mg) obtenido en el Ejemplo A194(4), óxido de isobutileno (439 mg), carbonato de potasio (422 mg) y yoduro de sodio (457 mg) en N,N-dimetilformamida (6 mL) se agitó a 80 °C durante 9 h. Luego se añadió óxido de isobutileno (2,0 g) a la mezcla y la mezcla se agitó a 120 °C durante 14 h. Se agregó más óxido de isobutileno (2,0 g) a la mezcla y la mezcla se agitó a 120 °C durante 5 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 50:50, v/v) para dar un aceite incoloro (103 mg). El aceite incoloro obtenido (103 mg) se disolvió en etanol (0,5 mL) y tetrahidrofurano (0,5 mL), una solución acuosa 1 N de hidróxido de sodio (0,36 mL) se añadió a la solución y la mezcla se agitó a temperatura ambiente durante 30 min. El solvente se evaporó a presión reducida, se añadió agua (4 mL) al residuo y la mezcla se neutralizó con ácido

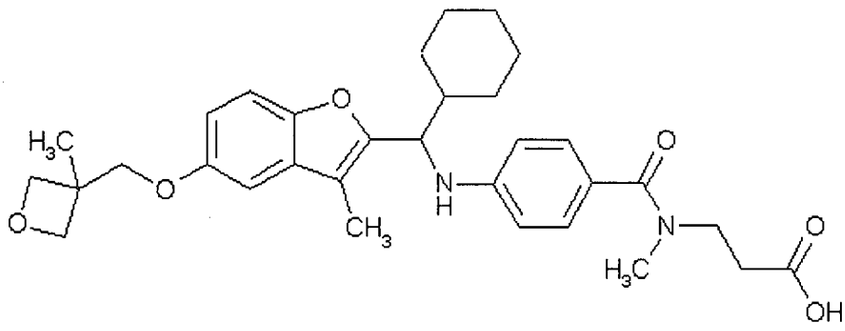
1680

clorhídrico 1 N (0,36 mL) bajo enfriamiento con hielo. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (88 mg, 26%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 - 1,27 (m, 6 H), 1,35 (s, 6 H), 1,47 - 1,91 (m, 5 H), 2,04 - 2,13 (m, 1 H), 2,21 (s, 3 H), 2,62 (t, J = 6,2 Hz, 2 H), 3,01 (s, 3 H), 3,67 (t, J = 6,6 Hz, 2 H), 3,82 (s, 2 H), 4,35 (d, J = 7,9 Hz, 1 H), 6,55 (d, J = 9,0 Hz, 2 H), 6,84 (dd, J = 8,7, 2,6 Hz, 1 H), 6,90 (d, J = 2,3 Hz, 1 H), 7,22 (d, J = 9,8 Hz, 2 H), 7,26 - 7,28 (m, 1 H).

Ejemplo A196

Ácido 3-[({4-[(ciclohexil{3-metil-5-[(3-metiloxetan-3-il)metoxi]-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



Una solución de 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (300 mg) obtenido en el Ejemplo A194(4), (3-metiloxetan-3-il)metanol (75 mg) y tributilfosfina (308 mg) en tetrahidrofurano (30 mL) se enfrió hasta 0 °C en un baño

1691

de hielo y 1,1'-(azodicarbonil)dipiperidina (308 mg) se añadió a la solución. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. A la mezcla de reacción se añadió hexano (60 mL). El material insoluble se filtró y el filtrado se concentró a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice (sílice NH, hexano-acetato de etilo 100:0 - 50:50, v/v) y luego instrumento de HPLC" preparativa: Gilson Inc., sistema de HPLC preparativa; columna: Develosyl ODS-UG-10, S-5 μm, 50 x 100 mm; solvente: SOLUCIÓN A; 0,1% de agua con contenido de ácido trifluoroacético, SOLUCIÓN B; 0,1% de acetonitrilo con contenido de ácido trifluoroacético, (SOLUCIÓN A:SOLUCIÓN B = 95:5 - 0:100); velocidad de flujo: 150 mL/min; método de detección: UV 220 nm". La fracción fraccionada se concentró y acetonitrilo se evaporó. Se añadió solución acuosa saturada de hidrógeno-carbonato de sodio (0 °C) a la capa acuosa y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar un aceite incoloro (100 mg). El aceite incoloro obtenido (100 mg) se disolvió en etanol (0,5 mL) y tetrahidrofurano (0,5 mL), una solución acuosa 1 N de hidróxido de sodio (0,34 mL) se añadió a la solución y la mezcla se agitó a temperatura ambiente durante 30 min. El solvente se evaporó a presión reducida, se añadió agua (4 mL) al residuo y la mezcla se neutralizó con ácido clorhídrico 1 N (0,34 mL) bajo enfriamiento con hielo y se agitó a 0 °C durante 30 min. El precipitado resultante se recogió por

1692

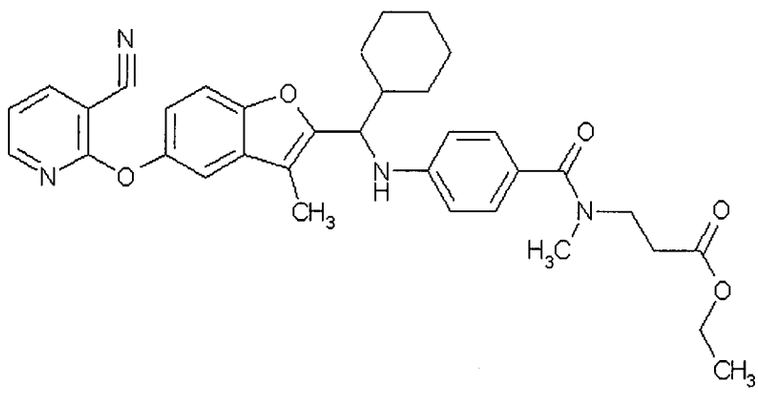
filtración y se secó para dar el compuesto del título (73 mg, 22%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 - 1,33 (m, 5 H), 1,45 (s, 3 H), 1,52 - 1,95 (m, 5 H), 2,09 (d, J = 8,7 Hz, 1 H), 2,22 (s, 3 H), 2,55 - 2,74 (m, 2 H), 3,03 (s, 3 H), 3,65 - 3,76 (m, 3 H), 4,05 (s, 2 H), 4,36 (d, J = 7,9 Hz, 1 H), 4,47 (d, J = 6,0 Hz, 2 H), 4,64 (d, J = 5,7 Hz, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,80 - 6,89 (m, 1 H), 6,92 (d, J = 2,6 Hz, 1 H), 7,14 - 7,32 (m, 3 H).

Ejemplo A197

3-{[(4-{[{5-[(3-cianopiridin-2-il)oxi]-3-metil-1-benzofuran-2-

il}(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo



Una solución de 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-

il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (300 mg) obtenido en el Ejemplo A194(4), 2-cloro-3-cianopiridina (126 mg) y carbonato de potasio (125 mg) en N,N-dimetilformamida (3 mL) se agitó a 80 °C durante 2,5 h.

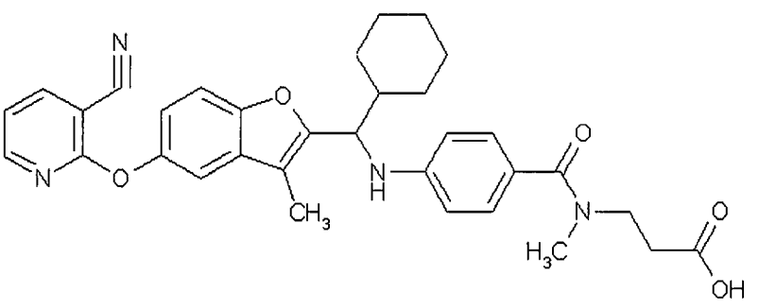
1693

Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 50:50, v/v) para dar el compuesto del título (250 mg, 69%) como una forma amorfa incolora.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,99 - 1,31 (m, 6 H), 1,48 - 1,96 (m, 6 H), 2,06 - 2,14 (m, 2 H), 2,23 (s, 3 H), 2,62 (t, J = 7,0 Hz, 2 H), 3,02 (s, 3 H), 3,71 (t, J = 7,0 Hz, 2 H), 4,12 (q, J = 7,2 Hz, 2 H), 4,31 - 4,44 (m, 2 H), 6,56 (d, J = 8,3 Hz, 2 H), 6,98 - 7,11 (m, 2 H), 7,19 - 7,25 (m, 3 H), 7,40 (d, J = 8,7 Hz, 1 H), 8,00 (dd, J = 7,6, 1,9 Hz, 1 H), 8,29 (dd, J = 4,9, 1,9 Hz, 1 H).

Ejemplo A198

Ácido 3-{[(4-{[{5-[(3-cianopiridin-2-il)oxi]-3-metil-1-benzofuran-2-il}(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico




El 3-{[(4-{[{5-[(3-cianopiridin-2-il)oxi]-3-metil-1-benzofuran-2-

1694

il}(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propan oato de etilo (234 mg) obtenido en el Ejemplo A197 se disolvió en etanol (1,5 mL) y tetrahidrofurano (1,5 mL), solución acuosa 1 N de hidróxido de sodio (0,78 mL) se añadió a la solución y la mezcla se agitó a temperatura ambiente durante 30 min. El solvente se evaporó a presión reducida, se añadió agua (4 mL) y la mezcla se neutralizó con ácido clorhídrico 1 N (0,78 mL) bajo enfriamiento con hielo. El precipitado resultante se recogió por filtración y se secó. El residuo obtenido se purificó por HPLC preparativa "instrumento: Gilson Inc., sistema de HPLC preparativa; columna: Develosyl ODS-UG-10, S-5 μm, 50 x 100 mm; solvente: SOLUCIÓN A; 0,1% de agua con contenido de ácido trifluoroacético, SOLUCIÓN B; 0,1% de acetonitrilo con contenido de ácido trifluoroacético, (SOLUCIÓN A:SOLUCIÓN B = 95:5 - 0:100); velocidad de flujo: 150 mL/min; método de detección: UV 220 nm". A la fracción fraccionada se añadió solución saturada acuosa de carbonato ácido de sodio y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar el compuesto del título (73 mg, 33%) como una forma amorfa incolora.

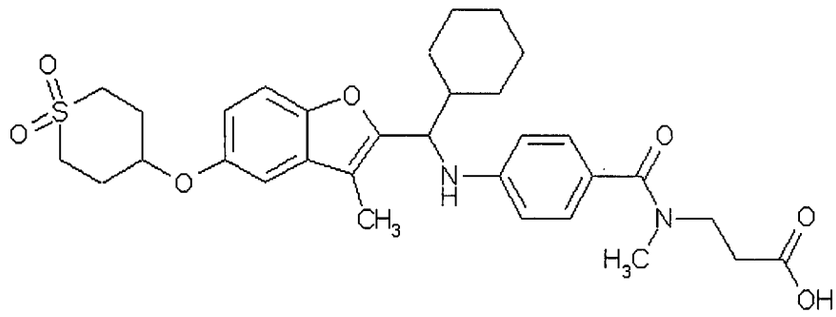
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,12 (br. s., 4 H), 1,42 - 1,91 (m, 6 H), 2,04 (s, 3 H), 2,20 (s, 3 H), 2,39 - 2,63 (m, 1 H), 2,89 - 3,03 (m, 3 H), 3,58 (m, 2 H), 4,37 (d, J = 8,0 Hz, 1 H), 6,54 (d, J = 8,3 Hz, 2 H), 6,94 - 7,10 (m, 2 H), 7,17 -

1695

7,24 (m, 3 H), 7,37 (d, J = 8,7 Hz, 1 H), 7,99 (dd, J = 7,6, 1,9 Hz, 1 H), 8,28 (d, J = 3,4 Hz, 1 H).

Ejemplo A199

Ácido 3-[({4-[(ciclohexil{5-[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)oxi]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico



(1) 4-metilbencensulfonato de 1,1-dioxidotetrahidro-2H-tiopiran-4-ilo

A una solución de 4-metilbencensulfonate de tetrahidro-2H-tiopiran-4-ilo (3,0 g) en ácido acético (9 mL) se añadió peróxido de hidrógeno al 30% (3 mL) y la mezcla se agitó a 50 °C durante 3,5 h. La mezcla de reacción se enfrió hasta temperatura ambiente, se añadió agua (30 mL) a la mezcla y la mezcla se agitó a 0 °C durante 5 min. El sólido obtenido se recogió por filtración y se lavó con agua para dar el compuesto del título (2,84 g, 85%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,26 - 2,36 (m, 4 H), 2,47 (s, 3 H), 2,84 - 3,00 (m, 2 H), 3,10 - 3,43 (m, 2 H), 4,74 - 4,86 (m, 1 H), 7,38 (d, J = 8,0 Hz, 2 H), 7,81 (d, J = 8,3 Hz, 2 H).

1696

(2) ácido 3-[({4-[(ciclohexil{5-[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)oxi]-3-metil-1-benzofuran-2-il}metil)amino]fenil}carbonil)(metil)amino]propanoico

Una solución de 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (400 mg) obtenido en el Ejemplo A194(4), 4-metilbencensulfonato de 1,1-dioxidotetrahidro-2H-tiopiran-4-ilo (593 mg) sintetizado con anterioridad y trifostato de potasio (223 mg) en N,N-dimetilformamida (4 mL) se agitó a 100 °C durante 14 h. Luego se añadieron 1,1-4-metilbencensulfonato de dioxidotetrahidro-2H-tiopiran-4-ilo (593 mg) y trifostato de potasio (112 mg) a la mezcla y la mezcla se agitó a 100 °C durante 2 h, luego a 120 °C durante 3 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 34:66, v/v) para dar una forma amorfa incolora (200 mg). La forma amorfa incolora (200 mg) se disolvió en etanol (1,5 mL) y tetrahidrofurano (1,5 mL) y una solución acuosa 1 N de hidróxido de sodio (0,64 mL) se añadió a la solución y la mezcla se agitó a temperatura ambiente durante 30 min. El solvente se evaporó a presión reducida, se añadió agua (4 mL) al residuo y la mezcla se neutralizó con ácido clorhídrico 1 N (0,64 mL) bajo enfriamiento con hielo y se agitó a 0 °C durante 30 min. El

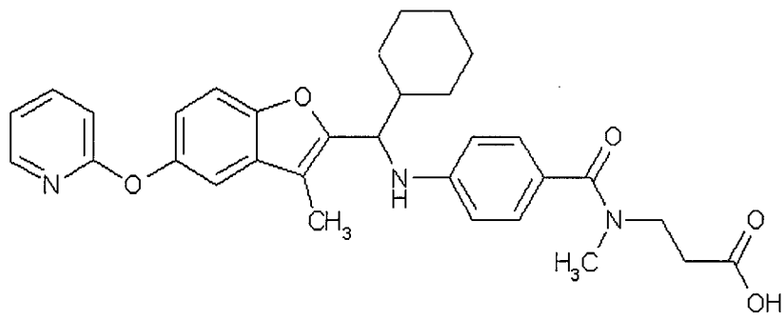
1697

precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (136 mg, 29%) como una forma amorfa incolora.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,99 - 2,00 (m, 8 H), 2,21 (s, 3 H), 2,31 - 2,73 (m, 10 H), 2,86 - 2,99 (m, 1 H), 3,03 (s, 3 H), 3,36 - 3,53 (m, 2 H), 3,65 - 3,76 (m, 2 H), 4,36 (d, J = 8,3 Hz, 1 H), 4,54 - 4,82 (m, 3 H), 6,55 (d, J = 8,3 Hz, 2 H), 6,78 - 6,87 (m, 1 H), 6,93 (d, J = 2,6 Hz, 1 H), 7,17 - 7,30 (m, 3 H).

Ejemplo A200

Ácido 3-[{[4-({ciclohexil[3-metil-5-(piridin-2-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico




Una solución de 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (300 mg) obtenido en el Ejemplo A194(4), 2-fluoropiridina (88 mg) y carbonato de potasio (126 mg) en N,N-dimetilformamida (3 mL) se agitó a 80 °C durante 8 h ten a temperatura ambiente durante 48 h. La 2-fluoropiridina (88 mg) se añadió a la mezcla y la mezcla se agitó a 120 °C

1698

durante 4 h. La 2-fluoropiridina (352 mg) se añadió a la mezcla y la mezcla se agitó a 120 °C durante 10 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 50:50, v/v) para dar un aceite incoloro (35 mg). El aceite obtenido (35 mg) se disolvió en tetrahidrofurano (0,5 mL) y una solución acuosa 1 N de hidróxido de sodio (0,12 mL) se añadió a la solución y la mezcla se agitó a 50 °C durante 1 h. El solvente se evaporó a presión reducida, se añadió agua (4 mL) al residuo y la mezcla se neutralizó con ácido clorhídrico 1 N (0,12 mL) bajo enfriamiento con hielo y se agitó a 0 °C durante 20 min. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (22 mg, 7%) como una forma amorfa incolora.

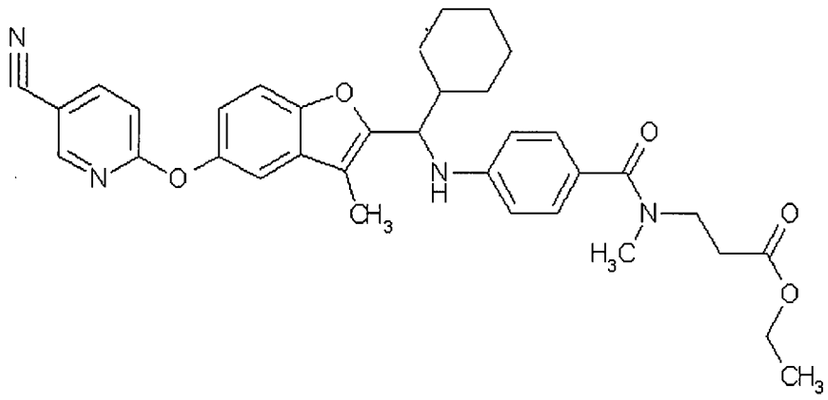
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 - 1,42 (m, 6 H), 1,51 - 1,96 (m, 5 H), 2,13 (br. s., 1 H), 2,19 (s, 3 H), 2,36 - 2,69 (m, 2 H), 3,01 (s, 3 H), 3,54 (br. s., 2 H), 4,39 (d, J = 7,9 Hz, 1 H), 6,58 (d, J = 8,7 Hz, 2 H), 6,88 - 7,05 (m, 3 H), 7,12 - 7,24 (m, 3 H), 7,33 (d, J = 8,7 Hz, 1 H), 7,65 - 7,74 (m, 1 H), 8,09 - 8,20 (m, 1 H).

Ejemplo A201

3-{[(4-{[{5-[(5-cianopiridin-2-il)oxi]-3-metil-1-benzofuran-2-

1694

il}(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propan oato de etilo



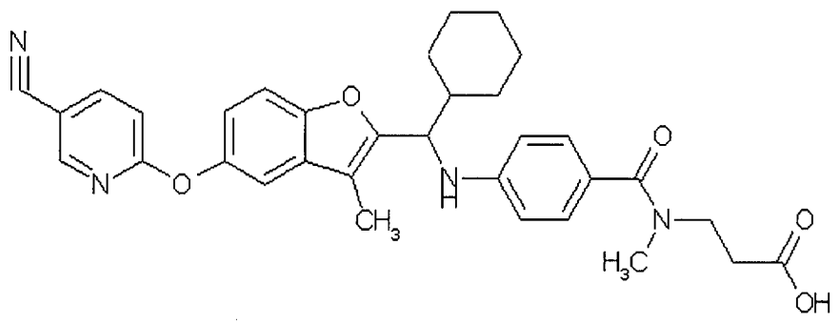
Una solución de 3-{[(4-{[ciclohexil(5-hidroxi-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (400 mg) obtenido en el Ejemplo A194(4), 2-cloro-5-cianopiridina (167 mg) y carbonato de potasio (168 mg) en N,N-dimetilformamida (4 mL) se agitó a 80 °C durante 14 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 50:50, v/v) para dar el compuesto del título (340 mg, 70%) como una forma amorfa incolora.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,01 - 1,30 (m, 8 H), 1,55 - 1,96 (m, 5 H), 2,09 - 2,15 (m, 1 H), 2,22 (s, 3 H), 2,62 (t, J = 6,8 Hz, 2 H), 3,03 (s, 3 H), 3,71 (t, J = 7,0 Hz, 2 H), 4,04 - 4,18 (m, 2 H), 4,27 - 4,48 (m, 2 H), 6,56 (d, J = 8,7

Hz, 2 H), 6,90 - 7,07 (m, 2 H), 7,17 (d, J = 2,3 Hz, 1 H), 7,22 (d, J = 8,7 Hz, 2 H), 7,40 (d, J = 8,7 Hz, 1 H), 7,90 (dd, J = 8,7, 2,3 Hz, 1 H), 8,46 (d, J = 2,3 Hz, 1 H).

Ejemplo A202

Ácido 3-{[(4-{[{5-[(5-cianopiridin-2-il)oxi]-3-metil-1-benzofuran-2-il}(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoico



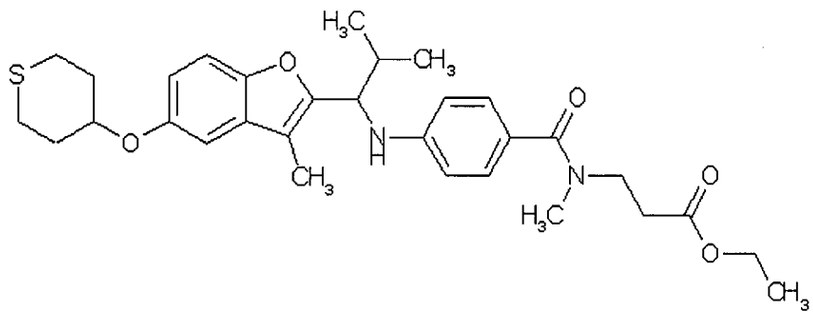
El 3-{[(4-{[{5-[(5-cianopiridin-2-il)oxi]-3-metil-1-benzofuran-2-il}(ciclohexil)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (300 mg) obtenido en el Ejemplo A201 se disolvió en tetrahidrofurano (4,0 mL) y solución acuosa 1 N de hidróxido de sodio (1,1 mL) se añadió a la solución y la mezcla se agitó a 50 °C durante 1 h. El solvente se evaporó a presión reducida, se añadió agua (4 mL) al residuo y la mezcla se neutralizó con ácido clorhídrico 1 N (1,1 mL) bajo enfriamiento con hielo y se agitó a 0 °C durante 30 min. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (271 mg, 87%) como una forma amorfa incolora.

1701

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,36 (m, 5 H), 1,52 - 2,11 (m, 7 H), 2,22 (s, 3 H), 2,61 (br. s., 2 H), 3,03 (s, 3 H), 3,66 (br. s., 2 H), 4,39 (d, J = 7,9 Hz, 1 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,91 - 7,08 (m, 2 H), 7,12 - 7,25 (m, 3 H), 7,39 (d, J = 8,7 Hz, 1 H), 7,90 (dd, J = 8,7, 2,3 Hz, 1 H), 8,45 (d, J = 2,3 Hz, 1 H).

Ejemplo A203

3-(metil{[4-({2-metil-1-[3-metil-5-(tetrahidro-2H-tiopiran-4-iloxi)-1-benzofuran-2-il]propil}amino)fenil]carbonil}amino)propanoato de etilo



(1)1-(5-hidroxi-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ona

La 1-[5-(benciloxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ona (4,0 g) sintetizada en el Ejemplo A85(1) se disolvió en etanol (80 mL) y complejo de carbono de paladio-etilendiamina (400 mg) se añadió a la solución a temperatura ambiente. La mezcla de reacción se agitó bajo una atmósfera de hidrógeno (1 atm) a temperatura ambiente durante 9,5 h. El catalizador se filtró y el filtrado se concentró a presión reducida para dar el compuesto del título (2,82 g, 100%) en forma de un sólido incoloro.

1702

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,24 (d, J = 6,8 Hz, 6 H), 2,55 (s, 3 H), 3,48 - 3,63 (m, 1 H), 6,95 - 7,08 (m, 2 H), 7,32 - 7,40 (m, 1 H).

(2) 2-metil-1-[3-metil-5-(tetrahidro-2H-tiopiran-4-iloxi)-1-benzofuran-2-il]propan-1-ona

Una solución de 1-(5-hidroxi-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ona (1,0 g) sintetizado con anterioridad, 4-metilbencensulfonato de tetrahidro-2H-tiopiran-4-ilo (2,99 g) y trifostato de potasio (1,26 g) en N,N-dimetilformamida (10 mL) se agitó a 80 °C durante 3 h, luego a 100 °C durante 14 h. El 4-metilbencensulfonato de tetrahidro-2H-tiopiran-4-ilo (2,99 g) se añadió a la mezcla y la mezcla se agitó a 100 °C durante 20 min. El trifostato de potasio (600 mg) se añadió a la mezcla y la mezcla se agitó a 100 °C durante 2 h, luego a 120 °C durante 3 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 90:10, v/v) para dar el compuesto del título (886 mg, 61%) en forma de un aceite anaranjado.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,23 (d, J = 6,8 Hz, 5 H), 1,82 - 2,29 (m, 4 H), 2,49 - 2,68 (m, 6 H), 2,88 - 3,00 (m, 2 H), 3,38 - 3,71 (m, 1 H), 4,25 - 4,50 (m, 1 H), 6,99 - 7,16 (m, 2 H), 7,40 (d, J = 9,5 Hz, 1 H).

1703

(3) 2-metil-1-[3-metil-5-(tetrahidro-2H-tiopiran-4-iloxi)-1-benzofuran-2-il]propan-1-ol

La 2-metil-1-[3-metil-5-(tetrahidro-2H-tiopiran-4-iloxi)-1-benzofuran-2-il]propan-1-ona (849 mg) sintetizada con anterioridad se disolvió en metanol (3 mL)-tetrahidrofurano (15 mL) y tetraborohidrato de sodio (90%) (202 mg) se añadió a la solución a 0 °C. La mezcla de reacción se agitó a 0 °C durante 30 min. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 85:15, v/v) para dar el compuesto del título (621 mg, 73%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,82 (d, J = 6,8 Hz, 3 H), 1,12 (d, J = 6,4 Hz, 3 H), 1,92 - 2,13 (m, 2 H), 2,16 - 2,27 (m, 6 H), 2,48 - 2,70 (m, 2 H), 2,89 - 3,01 (m, 2 H), 4,28 - 4,37 (m, 1 H), 4,46 (dd, J = 8,3, 6,0 Hz, 1 H), 6,87 (dd, 1 H), 6,96 (d, J = 2,6 Hz, 1 H), 7,30 (d, J = 8,7 Hz, 1 H).

(4) 3-(metil{[4-({2-metil-1-[3-metil-5-(tetrahidro-2H-tiopiran-4-iloxi)-1-benzofuran-2-il]propil}amino)fenil]carbonil}amino)propanoato de etilo

A una solución de 2-metil-1-[3-metil-5-(tetrahidro-2H-tiopiran-4-iloxi)-1-benzofuran-2-il]propan-1-ol (621 mg) obtenida con anterioridad en tetrahidrofurano (5 mL) se añadió cloruro de tionilo (0,17 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante

1704

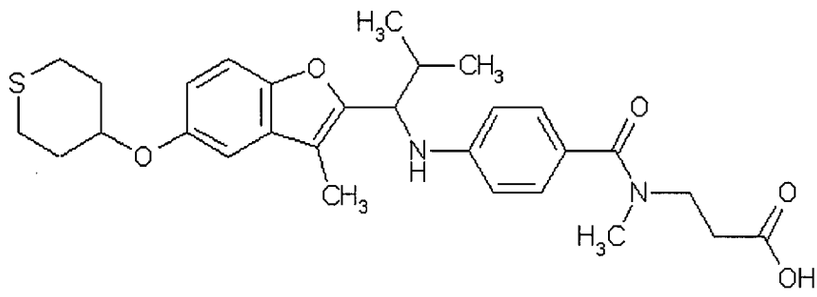
2 h. A la mezcla de reacción se añadió solución acuosa de carbonato ácido de sodio y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar un aceite incoloro (648 mg). Al aceite incoloro obtenido (648 mg) se añadieron 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (509 mg) obtenido en el Ejemplo 2 (2), yoduro de sodio (581 mg), carbonato de sodio (411 mg) y N,N-dimetilacetamida (5 mL) y la mezcla se agitó a 80 °C durante 19 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 50:50, v/v) para dar el compuesto del título (495 mg, 46%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,92 (d, J = 6,8 Hz, 3 H), 1,13 (d, J = 6,8 Hz, 3 H), 1,21 - 1,30 (m, 3 H), 1,95 - 2,09 (m, 2 H), 2,13 - 2,27 (m, 6 H), 2,49 - 2,67 (m, 4 H), 2,87 - 2,96 (m, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,2 Hz, 2 H), 4,07 - 4,16 (m, 2 H), 4,26 - 4,36 (m, 3 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,83 (dd, J = 8,7, 2,6 Hz, 1 H), 6,91 (d, J = 2,6 Hz, 1 H), 7,16 - 7,25 (m, 3 H).

Ejemplo A204

Ácido 3-(metil{[4-({2-metil-1-[3-metil-5-(tetrahidro-2H-tiopiran-4-iloxi)-1-benzofuran-2-il]propil}amino)fenil]carbonil}amino)propanoico

1705



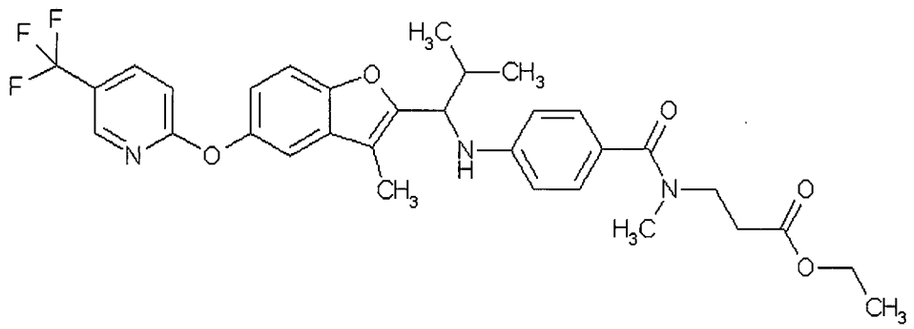
El 3-(metil{[4-({2-metil-1-[3-metil-5-(tetrahidro-2H-tiopiran-4-iloxi)-1-benzofuran-2-il]propil}amino)fenil]carbonil}amino)propanoato de etilo (485 mg) sintetizado en el Ejemplo A203 se disolvió en etanol (2,0 mL) y tetrahidrofurano (2,0 mL) y solución acuosa 1 N de hidróxido de sodio (1,96 mL) se añadió a la solución y la mezcla se agitó a temperatura ambiente durante 0,5 h. El solvente se evaporó a presión reducida, se añadió agua (4 mL) al residuo y la mezcla se neutralizó con ácido clorhídrico 1 N (1,96 mL) bajo enfriamiento con hielo y se agitó durante 30 min. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (421 mg, 91%) como una forma amorfa incolora.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 (d, J = 6,8 Hz, 3 H), 1,12 (d, J = 6,8 Hz, 3 H), 1,96 - 2,07 (m, 2 H), 2,15 - 2,28 (m, 6 H), 2,48 - 2,71 (m, 5 H), 3,02 (s, 3 H), 3,62 - 3,75 (m, 2 H), 4,21 - 4,35 (m, 2 H), 4,55 - 4,73 (m, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,83 (dd, J = 8,7, 2,7 Hz, 1 H), 6,91 (d, J = 2,7 Hz, 1 H), 7,20 - 7,26 (m, 3 H).

Ejemplo A205

1706

3-{metil[(4-{[2-metil-1-(3-metil-5-{[5-(trifluorometil)piridin-2-il]oxi}-1-benzofuran-2-il)propil]amino}fenil)carbonil]amino}propanoato de etilo



(1)2-metil-1-(3-metil-5-{[5-(trifluorometil)piridin-2-il]oxi}-1-benzofuran-2-il)propan-1-ona

Una solución de 1-(5-hidroxi-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ona (900 mg) sintetizada en el Ejemplo A203(1), 2-cloro-5-(trifluorometil)piridina (898 mg) y carbonato de potasio (854 mg) en N,N-dimetilformamida (5 mL) se agitó a 120 °C durante 1 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 90:10, v/v) para dar el compuesto del título (1,23 g, 82%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,25 (d, J = 6,8 Hz, 6 H), 2,58 (s, 3 H), 3,47 - 3,71 (m, 1 H), 7,06 (d, J = 8,7 Hz, 1 H), 7,21 - 7,29 (m, 1 H), 7,42 (d, J = 2,6 Hz, 1 H), 7,55 (d, J = 8,7 Hz, 1 H), 7,92 (dd, J = 8,7, 1,9 Hz, 1 H), 8,43 (s, 1 H).

1707

(2) 2-metil-1-(3-metil-5-{[5-(trifluorometil)piridin-2-il]oxi}-1-benzofuran-2-il)propan-1-ol

La 2-metil-1-(3-metil-5-{[5-(trifluorometil)piridin-2-il]oxi}-1-benzofuran-2-il)propan-1-ona (1,22 g) sintetizada con anterioridad se disolvió en metanol (40 mL)-tetrahidrofurano (4 mL) y el tetraborohidrato de sodio (90%)(253 mg) se añadió a la solución a 0 °C. La mezcla de reacción se agitó a 0 °C durante 2 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar el compuesto del título (1,22 g, 100%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,85 (d, 3 H), 1,13 (d, J = 6,4 Hz, 3 H), 1,98 - 2,04 (m, 1 H), 2,15 - 2,30 (m, 4 H), 4,50 (dd, J = 7,9, 3,8 Hz, 1 H), 6,94 - 7,09 (m, 2 H), 7,24 (d, J = 2,3 Hz, 1 H), 7,45 (d, J = 9,0 Hz, 1 H), 7,89 (dd, J = 8,7, 2,3 Hz, 1 H), 8,45 (s, 1 H).

(3) 3-{metil[(4-{[2-metil-1-(3-metil-5-{[5-(trifluorometil)piridin-2-il]oxi}-1-benzofuran-2-il)propil]amino}fenil)carbonil]amino}propanoato de etilo

A una solución de 2-metil-1-(3-metil-5-{[5-(trifluorometil)piridin-2-il]oxi}-1-benzofuran-2-il)propan-1-ol (776 mg) obtenido con anterioridad en tetrahidrofurano (5 mL) se añadió cloruro de tionilo (0,19 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 3 h. A la mezcla de reacción se añadió solución acuosa de carbonato ácido de sodio y la mezcla se

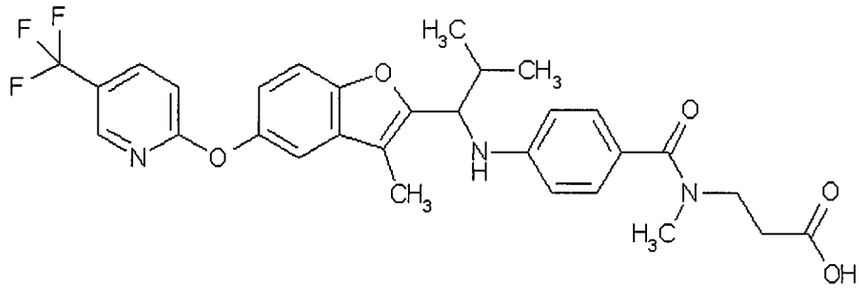
1708

extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. Al residuo obtenido se añadieron 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (557 mg) obtenido en el Ejemplo 2 (2), yoduro de sodio (636 mg), carbonato de sodio (449 mg) y N,N-dimetilacetamida (5 mL) y la mezcla se agitó a 80 °C durante 14 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 50:50, v/v) para dar el compuesto del título (436 mg, 34%) en forma de un compuesto amorfo amarillo.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 (d, J = 6,4 Hz, 3 H), 1,15 (d, J = 6,8 Hz, 3 H), 1,21 - 1,29 (m, 3 H), 1,60 (s, 3 H), 2,20 - 2,31 (m, 4 H), 2,62 (t, J = 6,8 Hz, 2 H), 3,72 (t, J = 7,2 Hz, 2 H), 4,12 (q, J = 7,2 Hz, 2 H), 4,34 (d, 2 H), 6,58 (d, 2 H), 6,99 (td, J = 5,8, 3,0 Hz, 2 H), 7,15 - 7,25 (m, 3 H), 7,39 (d, J = 9,0 Hz, 1 H), 7,88 (dd, J = 8,7, 2,3 Hz, 1 H), 8,43 (d, J = 2,6 Hz, 1 H).

Ejemplo A206

Ácido 3-{metil[(4-{[2-metil-1-(3-metil-5-{[5-(trifluorometil)piridin-2-il]oxi}-1-benzofuran-2-il)propil]amino}fenil)carbonil]amino}propanoico

1709



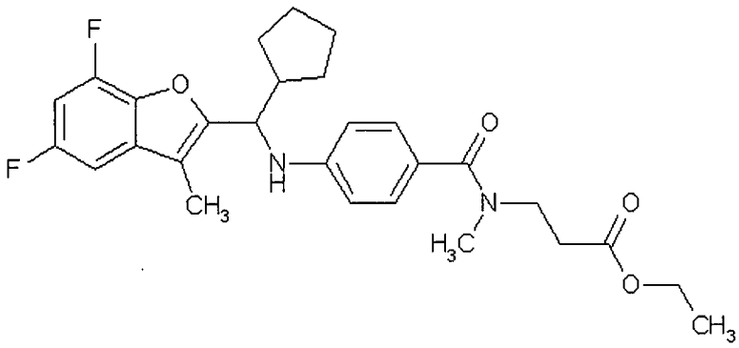
El 3-{metil[(4-{[2-metil-1-(3-metil-5-{[5-(trifluorometil)piridin-2-il]oxi}-1-benzofuran-2-il)propil]amino}fenil)carbonil]amino}propanoato de etilo (425 mg) sintetizado en el Ejemplo A205 se disolvió en tetrahidrofurano (4,0 mL), una solución acuosa 1 N de hidróxido de sodio (1,4 mL) se añadió a la solución y la mezcla se agitó a 50 °C durante 1,5 h. El solvente se evaporó a presión reducida, se añadió agua (4 mL) al residuo y la mezcla se neutralizó con ácido clorhídrico 1 N (1,4 mL) bajo enfriamiento con hielo y se agitó durante 20 min. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (378 mg, 94%) como una forma amorfa incolora.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 (d, J = 6,8 Hz, 3 H), 1,14 (d, J = 6,4 Hz, 3 H), 2,16 - 2,30 (m, 4 H), 2,52 (br. s., 2 H), 2,99 (s, 3 H), 3,62 (br. s., 2 H), 4,34 (d, J = 7,5 Hz, 1 H), 6,57 (d, J = 8,7 Hz, 2 H), 6,89 - 7,05 (m, 2 H), 7,14 - 7,25 (m, 3 H), 7,37 (d, J = 9,0 Hz, 1 H), 7,89 (dd, J = 8,9, 2,4 Hz, 1 H), 8,42 (s, 1 H).

Ejemplo A207

1710

3-{[(4-{[ciclopentil(5,7-difluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo



(1) ácido (2-acetil-4,6-difluorofenoxi)acético

Una solución de 3',5'-difluoro-2'-hidroxiacetofenona (5,0 g), bromoacetato de metilo (4,89 g) y carbonato de potasio (6,01 g) en N,N-dimetilformamida (50 mL) se agitó a temperatura ambiente durante 4 h. El material insoluble se filtró, se añadió ácido clorhídrico 1 N al filtrado y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un aceite marrón. Al aceite obtenido se añadieron tetrahidrofurano (60 mL), etanol (60 mL) y solución acuosa 1 N de hidróxido de sodio (60 mL) y la mezcla se agitó a temperatura ambiente durante 30 min. El solvente se concentró a presión reducida, ácido clorhídrico 1 N (60 mL) se añadió y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida

1711

para dar el compuesto del título (6,67 g, 100%) en forma de un sólido amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,67 (s, 3 H), 4,81 (s, 2 H), 7,01 - 7,12 (m, 1 H), 7,20 - 7,26 (m, 1 H), 9,19 (br. s., 1 H).

(2) 5,7-difluoro-3-metil-1-benzofurano

Una mezcla de ácido (2-acetil-4,6-difluorofenoxi)acético (6,60 g) obtenido con anterioridad, acetato de sodio (11,76 g) y anhídrido acético (40 mL) se agitó a 110 °C durante 8 h. La mezcla de reacción se enfrió hasta temperatura ambiente, se añadió agua a la mezcla y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con solución saturada acuosa de carbonato ácido de sodio, salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (sílice NH, hexano) para dar el compuesto del título (2,42 g, 50%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 2,21 (s, 3 H), 6,70 - 6,90 (m, 1 H), 6,97 (dd, J = 8,0, 2,3 Hz, 1 H), 7,46 (s, 1 H).

(3) ciclopentil(5,7-difluoro-3-metil-1-benzofuran-2-il)metanona

A una solución de 5,7-difluoro-3-metil-1-benzofurano (1,0 g) sintetizado con anterioridad y cloruro de ciclopentancarbonilo (867 mg) en nitrometano (20 mL) se añadió cloruro de aluminio (anhidro) (1,19 g) a 0 °C y la mezcla se agitó durante 2 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa

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orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 95:5, v/v) para dar el compuesto del título (1,25 g, 80%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,62 - 2,16 (m, 8 H), 2,57 (s, 3 H), 3,66 - 3,85 (m, 1 H), 6,90 - 7,05 (m, 1 H), 7,10 (dd, J = 7,3, 2,8 Hz, 1 H).

(4) ciclopentil(5,7-difluoro-3-metil-1-benzofuran-2-il)metanol

La ciclopentil(5,7-difluoro-3-metil-1-benzofuran-2-il)metanona (1,24 g) sintetizada con anterioridad se disolvió en metanol (4 mL)-tetrahidrofurano (20 mL) y el tetraborohidrato de sodio (90%)(355 mg) se añadió a la solución a 0 °C. La mezcla de reacción se agitó a 0 °C durante 2 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar el compuesto del título (1,18 g, 100%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,04 - 1,22 (m, 1 H), 1,43 - 1,75 (m, 6 H), 1,93 - 2,03 (m, 2 H), 2,22 (s, 3 H), 2,40 - 2,63 (m, 1 H), 4,56 (dd, J = 9,0, 6,4 Hz, 1 H), 6,72 - 6,85 (m, 1 H), 6,87 - 6,95 (m, 1 H).

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(5) 3-{[(4-{[ciclopentil(5,7-difluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

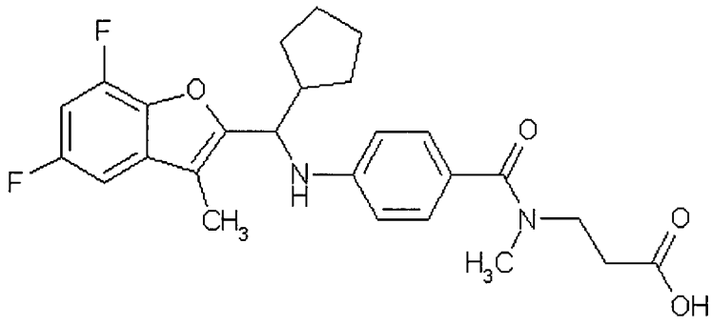
A una solución de ciclopentil(5,7-difluoro-3-metil-1-benzofuran-2-il)metanol (1,1 g) obtenida con anterioridad en tetrahidrofurano (10 mL) se añadió cloruro de tionilo (0,46 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 2 h. Luego se añadió cloruro de tionilo (0,46 mL) a la mezcla y la mezcla se agitó a temperatura ambiente durante 30 min. A la mezcla de reacción se añadió solución acuosa de hidrógeno-carbonato de sodio y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. Al residuo obtenido se añadieron 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (1,09 g) obtenido en el Ejemplo 2 (2), yoduro de sodio (1,24 g), carbonato de sodio (875 mg) y N,N-dimetilacetamida (10 mL) y la mezcla se agitó a 80 °C durante 2 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 50:50, v/v) para dar el compuesto del título (252 mg, 12%) en forma de un compuesto amorfo amarillo. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,24 (dt, J = 9,4, 7,1 Hz, 3 H), 1,46 - 1,79 (m, 7 H), 1,91 - 2,02 (m, 1 H), 2,25 (s, 3 H),

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2,42 - 2,67 (m, 3 H), 3,01 (s, 3 H), 3,70 (t, J = 7,2 Hz, 2 H), 4,04 - 4,16 (m, 2 H), 4,31 - 4,41 (m, 2 H), 6,56 (d, J = 8,7 Hz, 2 H), 6,68 - 6,79 (m, 1 H), 6,88 (dd, J = 8,0, 2,3 Hz, 1 H), 7,22 (d, J = 8,3 Hz, 2 H).

Ejemplo A208

Ácido 3-{[(4-{[ciclopentil(5,7-difluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico



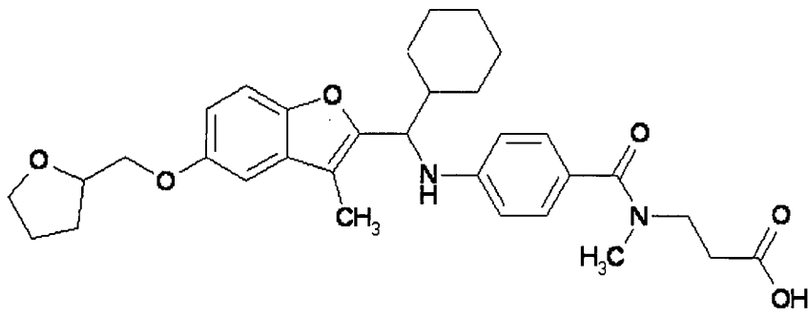

El 3-{[(4-{[ciclopentil(5,7-difluoro-3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (240 mg) sintetizado en el Ejemplo A207 se disolvió en etanol (1,0 mL)-tetrahidrofurano (1,0 mL), una solución acuosa 1 N de hidróxido de sodio (0,96 mL) se añadió a la solución y la mezcla se agitó a temperatura ambiente durante 30 min. El solvente se evaporó a presión reducida, se añadió agua (4 mL) al residuo y la mezcla se neutralizó con ácido clorhídrico 1 N (0,96 mL) bajo enfriamiento con hielo y se agitó durante 15 min. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (185 mg, 82%) como una forma amorfa incolora.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,16 - 1,39 (m, 1 H), 1,43 - 1,75 (m, 7 H), 1,86 - 2,06 (m, 1 H), 2,24 (s, 3 H), 2,38 - 2,56 (m, 1 H), 2,66 (t, J = 6,4 Hz, 2 H), 3,03 (s, 3 H), 3,70 (t, J = 6,8 Hz, 2 H), 4,37 (d, J = 9,4 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,68 - 6,80 (m, 1 H), 6,88 (dd, J = 7,9, 2,3 Hz, 1 H), 7,24 (d, J = 8,7 Hz, 2 H).

Ejemplo A209

Ácido 3-[{[4-({ciclohexil[3-metil-5-(tetrahidrofurano-2-ilmetoxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico




(1) ciclohexil[3-metil-5-(tetrahidrofurano-2-ilmetoxi)-1-benzofuran-2-il]metanona

Una solución de 1-(5-hidroxi-3-metil-1-benzofuran-2-il)-2-metilpropan-1-ona (300 mg) sintetizado en el Ejemplo A203(1), bromuro de tetrahidrofurfurilo (230 mg), carbonato de potasio (240 mg) en N,N-dimetilformamida (3 mL) se agitó a 80 °C durante 2 h, luego a 120 °C durante 4 h. El bromuro de tetrahidrofurfurilo (230 mg) se añadió a la mezcla y la mezcla se agitó a 120 °C durante 60 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de

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etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 90:10, v/v) para dar el compuesto del título (275 mg, 69%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,20 - 1,51 (m, 5 H), 1,68 - 2,17 (m, 9 H), 2,56 (s, 3 H), 3,20 - 3,39 (m, 1 H), 3,76 - 3,98 (m, 2 H), 4,02 (d, J = 5,3 Hz, 2 H), 4,24 - 4,37 (m, 1 H), 7,03 (d, J = 2,6 Hz, 1 H), 7,13 (dd, J = 9,0, 2,6 Hz, 1 H), 7,39 (d, J = 8,7 Hz, 1 H).

(2) ciclohexil[3-metil-5-(tetrahidrofurano-2-ilmetoxi)-1-benzofuran-2-il]metanol

La ciclohexil[3-metil-5-(tetrahidrofurano-2-ilmetoxi)-1-benzofuran-2-il]metanona (260 mg) sintetizada con anterioridad se disolvió en metanol (0,5 mL)-tetrahidrofurano (2,5 mL) y tetraborohidrato de sodio (90%)(64 mg) se añadió a la solución a 0 °C. La mezcla de reacción se agitó a 0 °C durante 2,5 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar el compuesto del título (235 mg, 90%) en forma de un aceite incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,77 - 1,46 (m, 8 H), 1,61 - 1,69 (m, 2 H), 1,72 - 2,01 (m, 6 H), 2,18 (s, 3 H), 3,78 - 3,89 (m, 1 H), 3,92 - 4,05 (m, 3 H), 4,22 - 4,39 (m, 1 H),

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4,50 (d, J = 8,7 Hz, 1 H), 6,87 - 6,92 (m, 1 H), 6,94 (d, J = 2,6 Hz, 1 H), 7,29 (d, J = 9,1 Hz, 1 H).

(3) ácido 3-[{[4-({ciclohexil[3-metil-5-(tetrahidrofurano-2-ilmetoxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico

A una solución de ciclohexil[3-metil-5-(tetrahidrofurano-2-ilmetoxi)-1-benzofuran-2-il]metanol (220 mg) obtenido con anterioridad en tetrahidrofurano (2 mL) se añadió cloruro de tionilo (70 µL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 2 h. A la mezcla de reacción se añadió solución acuosa de carbonato ácido de sodio y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. Al residuo obtenido se añadieron 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (168 mg) obtenido en el Ejemplo 2 (2), yoduro de sodio (192 mg), carbonato de sodio (136 mg) y N,N-dimetilacetamida (3,0 mL) y la mezcla se agitó a 80 °C durante 14 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 0:100, v/v) para dar una forma amorfa incolora (120 mg). La forma amorfa incolora obtenida (120 mg) se disolvió en etanol (1,0 mL)-tetrahidrofurano (1,0 mL), una solución acuosa 1 N de hidróxido de sodio (0,44 mL) se añadió

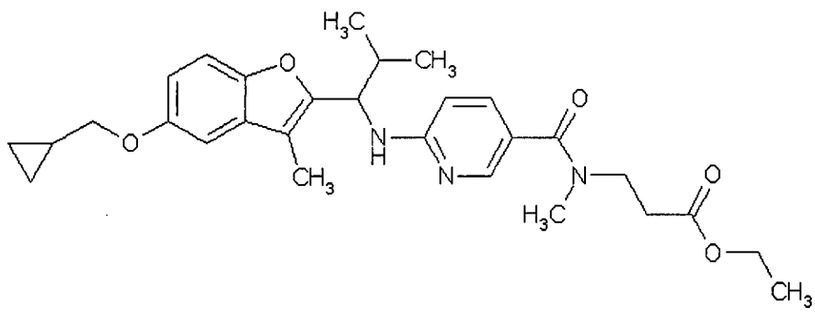
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a la solución y la mezcla se agitó a temperatura ambiente durante 1 h. El solvente se evaporó a presión reducida, agua (1 mL) se añadió al residuo y la mezcla se neutralizó con ácido clorhídrico 1 N (0,44 mL) bajo enfriamiento con hielo y se agitó durante 10 min. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (97 mg, 80%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,93 - 1,29 (m, 5 H), 1,47 - 2,14 (m, 11 H), 2,20 (s, 3 H), 2,54 - 2,72 (m, 2 H), 3,02 (s, 3 H), 3,67 (t, J = 6,4 Hz, 2 H), 3,77 - 3,90 (m, 1 H), 3,91 - 4,03 (m, 3 H), 4,19 - 4,32 (m, 1 H), 4,35 (d, J = 7,9 Hz, 1 H), 6,55 (d, J = 8,7 Hz, 2 H), 6,79 - 6,95 (m, 2 H), 7,16 - 7,25 (m, 3 H).

Ejemplo A210

3-[{[6-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-3-il]carbonil}(metil)amino]propanoato de etilo



(1) 6-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-3-carboxilato de metilo

A una solución de 1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ol (1,41 g) obtenido en el

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Ejemplo A75(3) en tetrahidrofurano (10 mL) se añadió cloruro de tionilo (0,45 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 2 h. A la mezcla de reacción se añadió solución acuosa de carbonato ácido de sodio enfriada con hielo hasta 0 °C y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar un sólido incoloro (1,42 g). Al sólido incoloro obtenido (710 mg) se añadieron 6-aminopiridin-3-carboxilato de metilo (411 mg), yoduro de sodio (770 mg), carbonato de sodio (545 mg) y N,N-dimetilacetamida (6 mL) y la mezcla se agitó a 80 °C durante 22 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 50:50, v/v) para dar el compuesto del título (265 mg, 25%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,33 - 0,39 (m, 2 H), 0,60 - 0,69 (m, 2 H), 0,88 - 0,95 (m, 3 H), 1,10 (d, J = 6,8 Hz, 3 H), 2,94 (s, 3 H), 3,01 (s, 3 H), 3,82 - 3,88 (m, 4 H), 5,01 (t, 1 H), 5,40 (d, J = 8,7 Hz, 1 H), 6,34 (d, J = 8,3 Hz, 1 H), 6,85 - 6,95 (m, 2 H), 7,21 - 7,27 (m, 1 H), 7,91 (dd, J = 9,0, 2,3 Hz, 1 H), 8,74 (d, J = 1,9 Hz, 1 H).

(2) ácido 6-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-3-carboxílico

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A una mezcla de 6-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-3-carboxilato de metilo (260 mg) obtenido con anterioridad, tetrahidrofurano (1,2 mL) y etanol (1,2 mL) se añadió solución acuosa 1 N de hidróxido de sodio (1,2 mL) y la mezcla se agitó con calentamiento a reflujo durante 5 h. solución acuosa 1 N de hidróxido de sodio (1,2 mL) se añadió a la mezcla y la mezcla se agitó con calentamiento a reflujo durante 16 h. Una solución acuosa 8 N de hidróxido de sodio (1,2 mL) se añadió a la mezcla y la mezcla luego se agitó con calentamiento a reflujo durante 1 h. La mezcla de reacción se concentró a presión reducida, se añadió agua (4 mL) al residuo y ácido clorhídrico 1 N (10,8 mL) se añadió a la mezcla bajo enfriamiento con hielo y la mezcla se agitó durante 10 min. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (145 mg, 58%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,31 - 0,37 (m, 2 H), 0,61 - 0,66 (m, 2 H), 0,94 (d, J = 6,8 Hz, 3 H), 1,15 (d, J = 6,8 Hz, 3 H), 1,21 - 1,37 (m, 1 H), 2,22 (s, 3 H), 2,31 - 2,48 (m, 1 H), 3,82 (d, J = 6,8 Hz, 2 H), 4,66 (br. s., 1 H), 6,36 (d, J = 8,7 Hz, 1 H), 6,79 - 6,92 (m, 2 H), 7,22 - 7,29 (m, 1 H), 8,05 (dd, J = 9,1, 1,9 Hz, 1 H), 8,75 (d, J = 1,9 Hz, 1 H).

(3) 3-[{[6-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-3-il]carbonil}(metil)amino]propanoato de etilo

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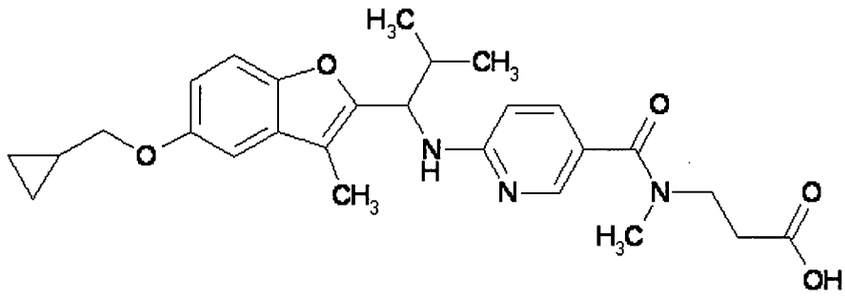
Una mezcla de ácido 6-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-3-carboxílico (145 mg) sintetizado con anterioridad, 3-(metilamino)propanoato de etilo (58 mg), monohidrato de 1-hidroxibenzotriazol (67 mg), trietilamina (122 µL), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (84 mg) y N,N-dimetilformamida (2 mL) se agitó a temperatura ambiente durante 18 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 0:100, v/v) para dar el compuesto del título (104 mg, 56%) como una forma amorfa incolora.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,26 - 0,49 (m, 2 H), 0,58 - 0,70 (m, 2 H), 0,86 - 1,00 (m, 3 H), 1,04 - 1,15 (m, 3 H), 1,18 - 1,31 (m, 4 H), 2,18 - 2,30 (m, 4 H), 2,63 (t, J = 6,8 Hz, 2 H), 3,06 (s, 3 H), 3,73 (t, J = 7,0 Hz, 2 H), 3,82 (d, J = 6,8 Hz, 2 H), 4,13 (q, J = 7,2 Hz, 2 H), 4,94 (t, J = 8,5 Hz, 1 H), 5,18 (d, J = 8,7 Hz, 1 H), 6,34 (d, J = 8,3 Hz, 1 H), 6,79 - 6,91 (m, 2 H), 7,22 - 7,26 (m, 1 H), 7,47 (dd, J = 8,3, 2,3 Hz, 1 H).

Ejemplo A211

Ácido 3-[{[6-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-3-il]carbonil}(metil)amino]propanoico

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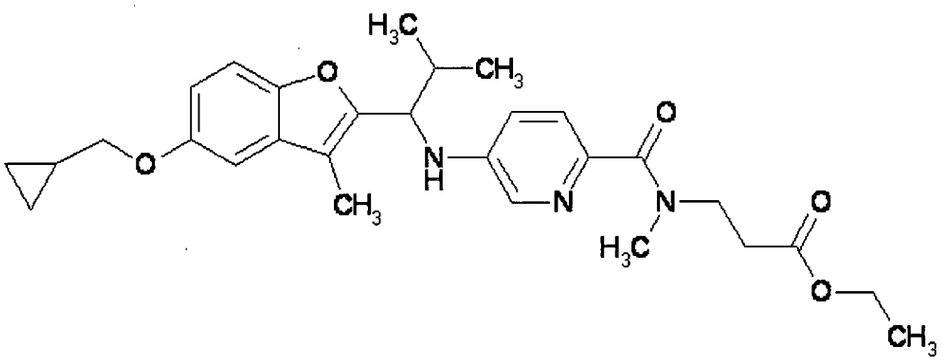


El 3-[{[6-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-3-il]carbonil}(metil)amino]propanoato de etilo (100 mg) sintetizado en el Ejemplo A210 se disolvió en etanol (0,5 mL)-tetrahidrofurano (0,5 mL), una solución acuosa 1 N de hidróxido de sodio (0,4 mL) se añadió a la solución y la mezcla se agitó a temperatura ambiente durante 2 h. El solvente se evaporó a presión reducida, se añadió agua (0,5 mL) al residuo y la mezcla se neutralizó con ácido clorhídrico 1 N (0,4 mL) bajo enfriamiento con hielo y la mezcla se agitó durante 20 min. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (77 mg, 80%) en forma de un sólido incoloro.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,30 - 0,43 (m, 2 H), 0,57 - 0,69 (m, 2 H), 0,92 (d, J = 6,4 Hz, 3 H), 1,15 (d, J = 6,4 Hz, 3 H), 1,23 - 1,35 (m, 1 H), 2,21 (s, 3 H), 2,30 - 2,43 (m, 1 H), 2,66 (t, J = 6,2 Hz, 2 H), 3,06 (s, 3 H), 3,70 - 3,77 (m, 2 H), 3,82 (d, J = 7,2 Hz, 2 H), 4,43 (br. s., 1 H), 6,38 (d, J = 9,1 Hz, 1 H), 6,80 - 6,91 (m, 2 H), 7,26 - 7,30 (m, 1 H), 7,57 (dd, J = 8,7, 1,9 Hz, 1 H), 8,10 (br. s., 1 H).

Ejemplo A212

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3-[{[5-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-2-il]carbonil}(metil)amino]propanoato de etilo



(1) 5-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-2-carboxilato de metilo

A una solución de 1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropan-1-ol (1,41 g) obtenido en el Ejemplo A75(3) en tetrahidrofurano (10 mL) se añadió cloruro de tionilo (0,45 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 2 h. A la mezcla de reacción se añadió solución acuosa de carbonato ácido de sodio enfriada hasta 0 °C y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró para dar un sólido incoloro (1,42 g). Al sólido incoloro obtenido (710 mg) se añadieron 5-aminopiridin-2-carboxilato de metilo (411 mg), yoduro de sodio (770 mg), carbonato de sodio (545 mg) y N,N-dimetilacetamida (6 mL) y la mezcla se agitó a 80 °C durante 2 h. Se añadió agua a la mezcla de reacción y la mezcla se

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extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de filtrar, el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 50:50, v/v) para dar el compuesto del título (424 mg, 40%) en forma de un aceite marrón.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,29 - 0,40 (m, 2 H), 0,60 - 0,69 (m, 2 H), 0,93 (d, J = 6,8 Hz, 3 H), 1,14 (d, J = 6,8 Hz, 3 H), 2,20 - 2,31 (m, 4 H), 3,82 (d, J = 6,8 Hz, 2 H), 3,91 (s, 3 H), 4,34 (t, J = 8,0 Hz, 1 H), 4,65 (d, J = 8,3 Hz, 1 H), 6,81 - 6,91 (m, 3 H), 7,23 (d, J = 9,5 Hz, 1 H), 7,89 (d, J = 8,3 Hz, 1 H), 8,10 (d, J = 2,7 Hz, 1 H).

(2) 5-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-2-carboxílico

A una mezcla de 5-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-2-carboxilato de metilo (410 mg) sintetizado con anterioridad, tetrahidrofurano (2,0 mL) y etanol (2,0 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,0 mL) y la mezcla se agitó con calentamiento a reflujo durante 14 h. La mezcla de reacción se concentró a presión reducida, se añadió agua (4 mL) al residuo, ácido clorhídrico 1 N (2 mL) se añadió bajo enfriamiento con hielo y la mezcla se agitó durante 20 min. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (323 mg, 80%) en forma de un sólido incoloro.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,35 (q, 2 H), 0,60 - 0,68 (m, 2 H), 0,94 (d, J = 6,8 Hz, 3 H), 1,15 (d, J = 6,8 Hz, 3 H), 1,24 - 1,35 (m, 1 H), 2,18 - 2,38 (m, 4 H), 3,82 (d, J = 7,2 Hz, 2 H), 4,35 (br. s., 1 H), 4,98 (br. s., 1 H), 6,82 - 6,90 (m, 2 H), 6,96 (dd, J = 8,7, 2,6 Hz, 1 H), 7,20 - 7,28 (m, 1 H), 7,95 (d, J = 8,7 Hz, 1 H), 8,08 (br. s., 1 H).

(3) 3-[{[5-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-2-il]carbonil}(metil)amino]propanoato de etilo

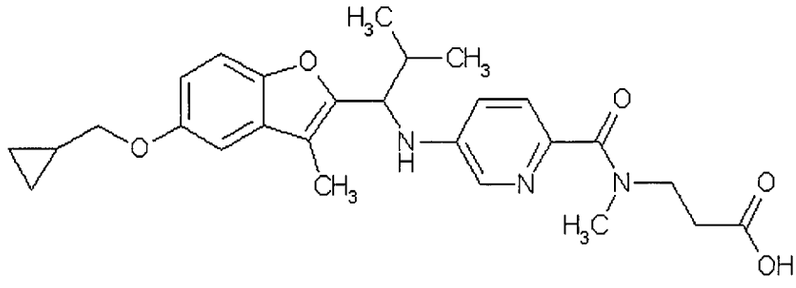
Una mezcla de ácido 5-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-2-carboxílico (311 mg) sintetizado con anterioridad, 3-(metilamino)propanoato de etilo (131 mg), monohidrato de 1-hidroxibenzotriazol (145 mg), trietilamina (265 µL), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (182 mg) y N,N-dimetilformamida (2 mL) se agitó a temperatura ambiente durante 16 h. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 0:100, v/v) para dar el compuesto del título (291 mg, 73%) como una forma amorfa incolora.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,31 - 0,39 (m, 2 H), 0,64 (q, J = 6,1 Hz, 2 H), 0,92 (d, J = 6,8 Hz, 3 H), 1,14 (d, 3 H), 1,22 - 1,31 (m, 3 H), 1,63 (s, 3 H), 2,17 - 2,30 (m, 4 H), 2,62 - 2,75 (m, 2 H), 3,71 - 3,93 (m, 4 H), 4,01 - 4,18 (m, 3

H), 4,24 - 4,36 (m, 1 H), 4,40 - 4,47 (m, 1 H), 6,75 - 6,92 (m, 3 H), 7,20 - 7,25 (m, 1 H), 7,53 (br. s., 1 H), 7,93 (br. s., 1 H).

Ejemplo A213

Ácido 3-[{[5-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-2-il]carbonil}(metil)amino]propanoico



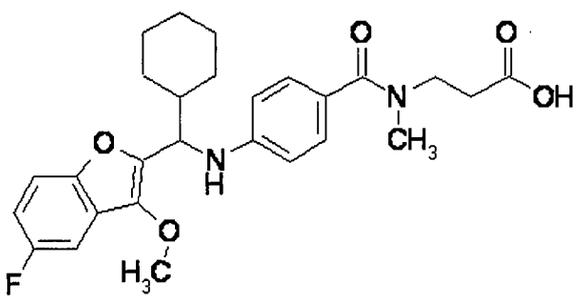
El 3-[{[5-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)piridin-2-il]carbonil}(metil)amino]propanoato de etilo (280 mg) sintetizado en el Ejemplo A212 se disolvió en etanol (1,0 mL)-tetrahidrofurano (1,0 mL), una solución acuosa 1 N de hidróxido de sodio (1,1 mL) se añadió a la solución y la mezcla se agitó a temperatura ambiente durante 1 h. El solvente se evaporó a presión reducida, agua (2,0 mL) se añadió al residuo y la mezcla se neutralizó con ácido clorhídrico 1 N (1,1 mL) bajo enfriamiento con hielo y se agitó durante 30 min. El precipitado resultante se recogió por filtración y se secó para dar el compuesto del título (238 mg, 90%) en forma de un sólido incoloro.

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$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,28 - 0,41 (m, 2 H), 0,57 - 0,68 (m, 2 H), 0,91 (d, J = 6,4 Hz, 3 H), 1,12 (d, J = 6,4 Hz, 3 H), 2,18 - 2,31 (m, 4 H), 2,77 (br. s., 2 H), 3,06 (br. s., 3 H), 3,68 - 3,77 (m, 2 H), 3,80 - 3,85 (m, 2 H), 4,29 (d, J = 7,6 Hz, 2 H), 4,66 (br. s., 1 H), 6,80 - 7,00 (m, 3 H), 7,24 (d, J = 8,7 Hz, 1 H), 7,61 (br. s., 1 H), 7,93 (br. s., 1 H).

Ejemplo A214

Ácido 3-{[(4-{[ciclohexil(5-fluoro-3-metoxi-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) ciclohexil(5-fluoro-3-hidroxi-1-benzofuran-2-il)metanona

La 1-(5-fluoro-2-hidroxifenil)etanona (4,0 g) se disolvió en acetonitrilo (80 mL). A la mezcla de reacción se añadieron carbonato de potasio (4,8 g) y 2-bromo-1-ciclohexiletanona (7,3 g) sintetizado en el Ejemplo A51(1) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 8 h. La mezcla de reacción se filtró a través de celite, se enjuagó con acetato de etilo y el filtrado se concentró a presión reducida. El residuo se disolvió en N,N-dimetilformamida (50 mL), 1,8-

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diazabiciclo[5,4,0]undec-7-eno (5,3 mL) se añadió a la solución y la mezcla se agitó con calentamiento a 110 °C durante 1 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se neutralizó con ácido clorhídrico 1 N y la mezcla se extrajo con éter dietílico. El extracto se concentró a presión reducida y el compuesto precipitado se recristalizó en éter diisopropílico-etanol para dar el compuesto objeto del título (4,7 g, 76%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,03 - 2,12 (m, 10 H), 3,00 - 3,26 (m, 1 H), 5,24 (s, 1 H), 7,14 - 7,50 (m, 3 H).

(2) ciclohexil(5-fluoro-3-metoxi-1-benzofuran-2-il)metanona

La ciclohexil(5-fluoro-3-hidroxi-1-benzofuran-2-il)metanona (3,0 g) sintetizada en el punto (1) antes mencionado se disolvió en tetrahidrofurano (15 mL) y N,N-dimetilformamida (15 mL). La mezcla de reacción se enfrió con hielo, se añadió hidruro de sodio (0,69 mg) a la solución y la mezcla se agitó durante 15 min. Se agregó dimetilsulfato (1,6 mL) a la mezcla y la mezcla se agitó a temperatura ambiente durante la noche. El solvente se evaporó a presión reducida, se añadió agua al residuo y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el precipitado se recristalizó en éter diisopropílico-hexano para dar el compuesto objeto del título (2,0 g, 63%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,16 - 2,03 (m, 10 H), 3,23 (tt, J = 11,2, 3,1 Hz, 1 H), 4,26 (s, 3 H), 7,20 - 7,54 (m, 3 H).

(3) ciclohexil(5-fluoro-3-metoxi-1-benzofuran-2-il)metanol

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La ciclohexil(5-fluoro-3-metoxi-1-benzofuran-2-il)metanona (2,0 g) sintetizada en el punto (2) antes mencionado se disolvió en tetrahidrofurano (15 mL) y metanol (3 mL) y el borohidruro de sodio (90%, 0,59 g) se añadió a la solución bajo enfriamiento con hielo. Se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se enfrió con hielo nuevamente y agua (2 mL) y ácido clorhídrico 1 N (10 mL) se añadieron cuidadosamente a la mezcla y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar un producto crudo (1,9 g, cuantitativo) del compuesto objeto del título en forma de un aceite amarillo. $^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,86 - 2,19 (m, 12 H), 3,97 (s, 3 H), 4,61 (d, J = 8,3 Hz, 1 H), 6,98 - 7,33 (m, 3 H).

(4) 3-{[(4-{[ciclohexil(5-fluoro-3-metoxi-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una solución (15 mL) de ciclohexil(5-fluoro-3-metoxi-1-benzofuran-2-il)metanol (1,9 g) sintetizado en el punto (3) antes mencionado en tetrahidrofurano se añadió cloruro de tionilo (0,48 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se enfrió con hielo y solución saturada acuosa de carbonato ácido de sodio (15 mL) se añadió cuidadosamente a la mezcla. La mezcla de reacción se agitó durante 10 min y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se

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concentró a presión reducida. El residuo se disolvió en dimetilacetamida (15 mL), se añadieron yoduro de sodio (0,98 g), carbonato de sodio (0,65 g) y 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (0,90 g) sintetizado en el Ejemplo 2(2) a la solución y la mezcla se agitó a 70 °C durante 4 h. Después de enfriar, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. El extracto se concentró a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo:hexano = 1:1, relación en volumen) para dar el compuesto objeto del título (0,30 g, 16%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 - 2,19 (m, 14 H), 2,61 (t, J = 7,2 Hz, 2 H), 3,01 (s, 3 H), 3,70 (t, J = 7,2 Hz, 2 H), 3,94 (s, 3 H), 4,11 (q, J = 7,2 Hz, 2 H), 4,30 - 4,46 (m, 2 H), 6,63 (d, J = 8,7 Hz, 2 H), 6,93 - 7,25 (m, 5 H).

(5) ácido 3-{[(4-{[ciclohexil(5-fluoro-3-metoxi-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico

El 3-{[(4-{[ciclohexil(5-fluoro-3-metoxi-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (0,30 g) sintetizado en el punto (4) antes mencionado se disolvió en etanol (5 mL), una solución acuosa 1 N de hidróxido de sodio (1,0 mL) se añadió a la solución a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 0,5 h. El etanol se evaporó a presión reducida y ácido clorhídrico 1 N (1,0 mL) se añadió al residuo. El precipitado se lavó con agua para dar el

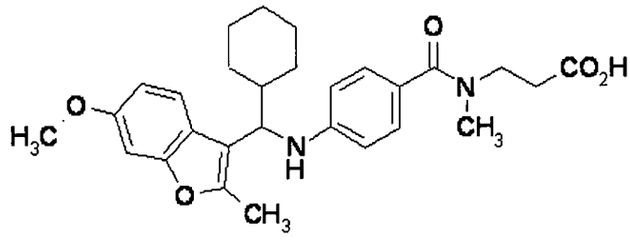
(731)

compuesto objeto del título (0,15 g, 52%) en forma de un sólido incoloro.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,94 - 2,20 (m, 11 H), 2,70 (t, J = 6,4 Hz, 2 H), 3,05 (s, 3 H), 3,71 (t, J = 6,4 Hz, 2 H), 3,94 (s, 3 H), 4,46 (d, J = 8,3 Hz, 1 H), 6,64 (d, J = 9,0 Hz, 2 H), 6,94 (td, J = 9,0, 2,6 Hz, 1 H), 7,14 - 7,31 (m, 4 H).

Ejemplo A215

Ácido 3-{[(4-{[ciclohexil(6-metoxi-2-metil-1-benzofuran-3-il)metil]amino}fenil)carbonil](metil)amino}propanoico




(1) ciclohexil(6-metoxi-2-metil-1-benzofuran-3-il)metanona

A una mezcla de 6-metoxi-2-metil-1-benzofurano (1,50 g), cloruro de ciclohexancarbonilo (1,36 mL) y nitrometano (15 mL) se añadió cloruro de aluminio (1,85 g) a 0 °C y la mezcla se agitó durante 1 h. Se añadió agua para neutralizar la reacción y la mezcla de reacción se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (0 - 10% de acetato de etilo/hexano) para dar el

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compuesto objeto del título (1,18 g, 47%) en forma de un aceite amarillo.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 1,20 - 1,62 (m, 5 H), 1,69 - 1,81 (m, 1 H), 1,82 - 2,02 (m, 4 H), 2,73 (s, 3 H), 2,95 - 3,09 (m, 1 H), 3,85 (s, 3 H), 6,93 (dd, J = 8,7, 2,2 Hz, 1 H), 6,97 (d, J = 2,2 Hz, 1 H), 7,68 (d, J = 8,7 Hz, 1 H).

(2) ciclohexil(6-metoxi-2-metil-1-benzofuran-3-il)metanol

A una mezcla de ciclohexil(6-metoxi-2-metil-1-benzofuran-3-il)metanona (1,18 g) sintetizado con anterioridad, metanol (1 mL) y tetrahidrofurano (10 mL) se añadió borohidruro de sodio (246 mg) a 0 °C y la mezcla se agitó durante 30 min. Se añadió ácido clorhídrico 1 N para neutralizar la reacción, el solvente orgánico se evaporó en un evaporador y el residuo se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (906 mg, 76%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,76 - 0,97 (m, 1 H), 0,99 - 1,38 (m, 4 H), 1,37 - 1,50 (m, 1 H), 1,51 - 1,72 (m, 2 H), 1,74 - 2,00 (m, 2 H), 2,11 - 2,24 (m, 1 H), 2,38 (s, 3 H), 3,83 (s, 3 H), 4,50 (d, J = 8,0 Hz, 1 H), 6,81 (dd, J = 8,5, 2,2 Hz, 1 H), 6,93 (d, J = 2,2 Hz, 1 H), 7,51 (d, J = 8,5 Hz, 1 H).

(3) 3-[cloro(ciclohexil)metil]-6-metoxi-2-metil-1-benzofurano

A una solución (10 mL) de ciclohexil(6-metoxi-2-metil-1-benzofuran-3-il)metanol (499 mg) sintetizado con anterioridad en tolueno se añadió cloruro de tionilo (159 µL) y la mezcla

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se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se vertió en solución saturada acuosa de carbonato ácido de sodio helada y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida para dar el compuesto objeto del título (530 mg, 99%) en forma de un aceite amarillo pálido.

$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,72 - 0,92 (m, 1 H), 0,97 - 1,40 (m, 4 H), 1,44 - 1,72 (m, 3 H), 1,76 - 1,89 (m, 1 H), 2,05 - 2,22 (m, 1 H), 2,29 - 2,46 (m, 4 H), 3,83 (s, 3 H), 4,74 (d, J = 9,3 Hz, 1 H), 6,84 (dd, J = 8,5, 2,4 Hz, 1 H), 6,93 (d, J = 2,4 Hz, 1 H), 7,55 (d, J = 8,5 Hz, 1 H).

(4) 3-{[(4-{[ciclohexil(6-metoxi-2-metil-1-benzofuran-3-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo

A una mezcla de 3-[cloro(ciclohexil)metil]-6-metoxi-2-metil-1-benzofurano (530 mg) sintetizado con anterioridad, 3-{[(4-aminofenil)carbonil](metil)amino}propanoato de etilo (498 mg) sintetizado en el Ejemplo 2(2) y N,N-dimetilformamida (10 mL) se añadieron yoduro de sodio (408 mg) y carbonato de sodio (288 mg) y la mezcla se agitó a 80 °C durante la noche. Se añadió solución acuosa saturada de cloruro de amonio para neutralizar la reacción y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (30 - 70% de

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acetato de etilo/hexano) para dar el compuesto objeto del título (781 mg, 85%) en forma de un sólido blanco.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 - 1,37 (m, 8 H), 1,54 - 1,96 (m, 5 H), 1,99 - 2,12 (m, 1 H), 2,42 (s, 3 H), 2,60 (t, J = 6,9 Hz, 2 H), 3,00 (s, 3 H), 3,69 (t, J = 6,9 Hz, 2 H), 3,82 (s, 3 H), 4,11 (q, J = 7,1 Hz, 2 H), 4,19 - 4,32 (m, 2 H), 6,47 (d, J = 8,5 Hz, 2 H), 6,79 (dd, J = 8,5, 2,2 Hz, 1 H), 6,91 (d, J = 2,2 Hz, 1 H), 7,17 (d, J = 8,5 Hz, 2 H), 7,40 (d, J = 8,5 Hz, 1 H).

(5) ácido 3-{[(4-{[ciclohexil(6-metoxi-2-metil-1-benzofuran-3-il)metil]amino}fenil)carbonil](metil)amino}propanoico

A una mezcla de 3-{[(4-{[ciclohexil(6-metoxi-2-metil-1-benzofuran-3-il)metil]amino}fenil)carbonil](metil)amino}propanoato de etilo (781 mg) sintetizado con anterioridad, tetrahidrofurano (5 mL) y etanol (5 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2,00 mL) y la mezcla se agitó a temperatura ambiente durante 1 h y se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y ácido clorhídrico 1 N (2,00 mL) se añadió a 0 °C. El precipitado resultante se recogió por filtración para dar el compuesto objeto del título (702 mg, 95%) en forma de un sólido blanco.
$^1$H RMN (300 MHz, $CDCl_3$) δ ppm 0,91 - 1,36 (m, 5 H), 1,57 - 1,97 (m, 5 H), 1,99 - 2,11 (m, 1 H), 2,41 (s, 3 H), 2,64 (t, J = 6,6 Hz, 2 H), 3,01 (s, 3 H), 3,68 (t, J = 6,6 Hz, 2 H), 3,81 (s, 3 H), 4,24 (d, J = 7,5 Hz, 1 H), 6,47 (d, J = 8,7 Hz, 2 H), 6,79 (dd, J = 8,7, 2,3 Hz, 1 H), 6,91 (d, J = 2,3

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Hz, 1 H), 7,18 (d, J = 8,7 Hz, 2 H), 7,40 (d, J = 8,7 Hz, 1 H).

Ejemplo experimental 1

La acción inhibitoria de fijación de glucagón del compuesto de la presente invención fue evaluada por el siguiente método.

(1) Clonación de gen de receptor de glucagón humano

El gen de receptor de glucagón humano fue clonado por reacción de PCR mediante el uso de cADN de páncreas humano listo Maraton (Clontech) como plantilla y el siguiente conjunto de cebadores.

GGR-U:

5'-AATAGAATTCATGCCCCCCTGCCAGCCACAG-3' (SEQ ID NO: 1)

GGR-L:

5'-CTAAGCGGCCGCTCAGAAGGGGCTCTCAGCCAATCT-3' (SEQ ID NO: 2)

Se realizó la reacción de PCR mediante el uso de polimerasa Advantage 2 (Clontech) y de acuerdo con el protocolo adjunto. El producto de PCR obtenido se sometió a electrofóresis en gel de agarosa (1%). Se recuperó del gel un fragmento de ADN de aproximadamente 1,4 kb que contiene un gen de receptor de glucagón y ser digirió con enzimas de restricción EcoRI y NotI. El ADN tratado con las enzimas de restricción se sometió a electroforesis en gel de agarosa (1%). Se recuperó un fragmento de ADN de aproximadamente 1,4 kb y se ligó a plásmido pMSRαneo digerido con las enzimas de restricción EcoRI y NotI para construir un ADN plásmido de expresión del receptor de glucagón de tipo humano "pMSRαneo/hGCGR". Se confirmó la secuencia de bases de un

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fragmento insertado y se confirmó la secuencia de bases coincidente con la secuencia objeto.

(2) Preparación de proteína de membrana de receptor de glucagón

Se expresó un receptor de glucagón de tipo humano mediante el uso de FreeStyle CHO Expression System (Invitrogen). Se realizó una expresión transitoria en células FreeStyle CHO mediante el uso de ADN de plásmido de expresión de receptor de glucagón de tipo humano "pMSRαneo/hGCGR" y de acuerdo con el manual adjunto a FreeStyle CHO Expression System. El ADN antes mencionado se transfectó y se cultivó con agitación durante 2 días (37 °C, 8% de $CO_2$, 125 rpm). Se centrifugaron 2400 ml de medio de cultivo a 2.000 rpm durante 10 min y se juntaron las células. Las células obtenidas se lavaron con PBS, se suspendieron en buffer de homogenado [10 mM de $NaHCO_3$ (pH 7,4), 1 mM de EDTA, totalmente libre de EDTA (Roche, 1 comprimido/50 ml)] y se rompieron con un disruptor celular de politrones (Kinematica AG). La solución de disrupción se centrifugó a 2.000 rpm durante 10 min y se juntó el sobrenadante. El sobrenadante se centrifugó a 35.000 rpm durante 60 min y el precipitado se suspendió en un buffer [20 mM de Tris-HCl (pH 7,4), 5 mM de EDTA, totalmente libre de EDTA (Roche, 1 comprimido/50 ml)] para dar una proteína de membrana de receptor de glucagón (452 mg).

(3) Medición de actividad inhibitoria de la fijación de glucagón

A cada cavidad de una placa de 96 cavidades (Corning Incorporated) se añadieron 25 µl de compuesto de prueba (que

(737

contiene 0,4% de DMSO), 50 µl de proteína de membrana de receptor de glucagón diluido con buffer de reacción [50 mM de Tris-HCl (pH 7,4), 5 mM de EGTA, 5 mM de cloruro de magnesio, 0,1% de BSA, 0,005% de Tween20] a 100 µg/ml y 25 µl de glucagón con marca radioactiva (receptor de glucagón de grado [$^{125}$I]; Perkin Elmer Inc.) diluido con buffer de reacción a 200 pM, por el cual se inició la reacción. La placa se dejó durante 90 min a temperatura ambiente. La solución de reacción se transfirió de la placa de reacción a una placa unifiltro de 96 cavidades GF/C (Perkin Elmer Inc.) mediante el uso de un cosechador de célula (Perkin Elmer Inc.) y la fracción de membrana se juntó en el filtro por succión. El filtro se remojó previamente en 2 mg/ml de polietilenimina para impedir la adsorción no específica del ligando rotulado. El filtro se lavó 4 veces con un buffer de reacción y se secó durante 2 h a 42 °C. A cada cavidad se añadió 25 µl de centellador (MicroScint0; Perkin Elmer Inc.) y se midió la cantidad de fluorescencia mediante el uso de un contador de centelleo de microplaca (TopCount NXT™; Perkin Elmer Inc.). Se calculó la actividad inhibidora de fijación de glucagón (valor $IC_{50}$) de la cavidad con el agregado de compuesto de prueba (que contiene 0,4% de DMSO), mediante el uso de una tasa de reacción de la cavidad añadida solamente con 0,4% de DMSO como 0% de tasa inhibitoria y la tasa de reacción de la cavidad con añadido de glucagón sin rotular (concentración final 1 µM) como 100% de tasa inhibitoria. Los resultados se muestran en la Tabla 1.

Tabla 1

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| Compuesto de prueba | Valor de $IC_{50}$ (nM) |
|---|---|
| Ejemplo 8 | 410 |
| Ejemplo 41 | 2300 |
| Ejemplo 61 | 320 |
| Ejemplo A3 | 1700 |
| Ejemplo A7 | 1800 |
| Ejemplo A12 | 210 |
| Ejemplo A17 | 230 |
| Ejemplo A49 | 640 |
| Ejemplo A53 | 570 |
| Ejemplo A73 | 900 |
| Ejemplo A78 | 280 |
| Ejemplo A83 | 84 |

Además, se calculó la tasa inhibitoria (%) de la cavidad con agregado de compuesto de prueba (10 µM; que contiene 0,4% de DMSO), mediante la tasa de reacción de la cavidad con agregado solamente de 0,4% de DMSO como 0% de tasa inhibitoria y la tasa de reacción de la cavidad con agregado de glucagón no rotulado (concentración final 1 µM) como 100% de tasa inhibitoria. Los resultados se muestran en la Tabla 2.

[Tabla 2-1]

Tabla 2

| compuesto de prueba | tasa inhibitoria (%) a 10 µM |
|---|---|
| Ejemplo 1 | 73 |
| Ejemplo 2 | 72 |
| Ejemplo 3 | 74 |
| Ejemplo 4 | 77 |

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| | |
|---|---|
| Ejemplo 5 | 73 |
| Ejemplo 6 | 75 |
| Ejemplo 7 | 72 |
| Ejemplo 8 | 75 |
| Ejemplo 9 | 74 |
| Ejemplo 10 | 76 |
| Ejemplo 11 | 73 |
| Ejemplo 12 | 74 |
| Ejemplo 13 | 71 |
| Ejemplo 14 | 71 |
| Ejemplo 15 | 72 |
| Ejemplo 16 | 63 |
| Ejemplo 17 | 80 |
| Ejemplo 18 | 72 |
| Ejemplo 19 | 80 |
| Ejemplo 20 | 79 |
| Ejemplo 21 | 77 |
| Ejemplo 22 | 61 |
| Ejemplo 23 | 71 |
| Ejemplo 24 | 73 |
| Ejemplo 25 | 78 |
| Ejemplo 26 | 72 |
| Ejemplo 27 | 70 |
| Ejemplo 28 | 71 |
| Ejemplo 29 | 77 |
| Ejemplo 30 | 75 |
| Ejemplo 31 | 67 |
| Ejemplo 32 | 59 |

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|---|---|
| Ejemplo 33 | 75 |
| Ejemplo 34 | 79 |
| Ejemplo 35 | 75 |
| Ejemplo 36 | 69 |

[Tabla 2-2]

Tabla 2 (continuación)

| compuesto de prueba | tasa inhibitoria (%) a 10 μM |
|---|---|
| Ejemplo 37 | 70 |
| Ejemplo 38 | 53 |
| Ejemplo 41 | 60 |
| Ejemplo 43 | 54 |
| Ejemplo 44 | 69 |
| Ejemplo 45 | 60 |
| Ejemplo 46 | 71 |
| Ejemplo 47 | 66 |
| Ejemplo 48 | 63 |
| Ejemplo 50 | 68 |
| Ejemplo 51 | 60 |
| Ejemplo 52 | 63 |
| Ejemplo 54 | 62 |
| Ejemplo 56 | 76 |
| Ejemplo 58 | 69 |
| Ejemplo 59 | 61 |
| Ejemplo 60 | 71 |
| Ejemplo 61 | 75 |
| Ejemplo 62 | 68 |
| Ejemplo 63 | 72 |
| Ejemplo 64 | 70 |

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| | |
|---|---|
| Ejemplo 65 | 64 |
| Ejemplo 66 | 74 |
| Ejemplo 67 | 72 |
| Ejemplo 68 | 66 |
| Ejemplo 70 | 75 |
| Ejemplo 71 | 71 |
| Ejemplo 72 | 51 |
| Ejemplo 73 | 59 |
| Ejemplo 75 | 61 |
| Ejemplo 76 | 68 |
| Ejemplo 77 | 55 |
| Ejemplo 78 | 69 |
| Ejemplo 79 | 67 |
| Ejemplo 81 | 82 |
| Ejemplo 82 | 78 |
| Ejemplo 83 | 78 |

[Tabla 2-3]

Tabla 2 (continuación)

| compuesto de prueba | tasa inhibitoria (%) a 10 μM |
|---|---|
| Ejemplo 84 | 76 |
| Ejemplo 85 | 68 |
| Ejemplo 86 | 76 |
| Ejemplo 87 | 64 |
| Ejemplo 88 | 71 |
| Ejemplo 89 | 62 |
| Ejemplo 90 | 66 |
| Ejemplo 91 | 71 |
| Ejemplo 92 | 56 |

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| | |
|---|---|
| Ejemplo A1 | 76 |
| Ejemplo A2 | 64 |
| Ejemplo A3 | 55 |
| Ejemplo A4 | 66 |
| Ejemplo A5 | 77 |
| Ejemplo A6 | 87 |
| Ejemplo A7 | 60 |
| Ejemplo A8 | 78 |
| Ejemplo A9 | 67 |
| Ejemplo A10 | 80 |
| Ejemplo A11 | 74 |
| Ejemplo A12 | 72 |
| Ejemplo A13 | 85 |
| Ejemplo A14 | 73 |
| Ejemplo A15 | 72 |
| Ejemplo A16 | 74 |
| Ejemplo A17 | 72 |
| Ejemplo A19 | 71 |
| Ejemplo A20 | 72 |
| Ejemplo A21 | 62 |
| Ejemplo A22 | 66 |
| Ejemplo A23 | 77 |
| Ejemplo A24 | 70 |
| Ejemplo A25 | 60 |
| Ejemplo A26 | 64 |
| Ejemplo A27 | 80 |
| Ejemplo A28 | 62 |
| Ejemplo A29 | 77 |

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[Tabla 2-4]

Tabla 2 (continuación)

| compuesto de prueba | tasa inhibitoria (%) a 10 μM |
|---|---|
| Ejemplo A30 | 76 |
| Ejemplo A31 | 62 |
| Ejemplo A32 | 72 |
| Ejemplo A33 | 76 |
| Ejemplo A34 | 75 |
| Ejemplo A35 | 71 |
| Ejemplo A36 | 73 |
| Ejemplo A37 | 78 |
| Ejemplo A38 | 56 |
| Ejemplo A39 | 78 |
| Ejemplo A41 | 86 |
| Ejemplo A43 | 80 |
| Ejemplo A44 | 82 |
| Ejemplo A46 | 78 |
| Ejemplo A47 | 67 |
| Ejemplo A48 | 66 |
| Ejemplo A49 | 86 |
| Ejemplo A51 | 71 |
| Ejemplo A52 | 64 |
| Ejemplo A53 | 83 |
| Ejemplo A54 | 52 |
| Ejemplo A55 | 90 |
| Ejemplo A56 | 76 |
| Ejemplo A57 | 85 |
| Ejemplo A59 | 77 |

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| | |
|---|---|
| Ejemplo A60 | 85 |
| Ejemplo A62 | 81 |
| Ejemplo A63 | 90 |
| Ejemplo A64 | 84 |
| Ejemplo A65 | 79 |
| Ejemplo A68 | 82 |
| Ejemplo A69 | 89 |
| Ejemplo A72 | 79 |
| Ejemplo A73 | 87 |
| Ejemplo A76 | 83 |
| Ejemplo A78 | 90 |
| Ejemplo A79 | 73 |

[Tabla 2-5]

Tabla 2 (continuación)

| compuesto de prueba | tasa inhibitoria (%) a 10 μM |
|---|---|
| Ejemplo A80 | 92 |
| Ejemplo A82 | 89 |
| Ejemplo A83 | 93 |
| Ejemplo A85 | 82 |
| Ejemplo A86 | 89 |
| Ejemplo A88 | 75 |
| Ejemplo A89 | 80 |
| Ejemplo A90 | 77 |
| Ejemplo A91 | 79 |
| Ejemplo A92 | 76 |
| Ejemplo A93 | 70 |
| Ejemplo A94 | 57 |
| Ejemplo A96 | 76 |

| | |
|---|---|
| Ejemplo A97 | 76 |
| Ejemplo A98 | 78 |
| Ejemplo A99 | 80 |
| Ejemplo A100 | 78 |
| Ejemplo A101 | 76 |
| Ejemplo A102 | 68 |
| Ejemplo A103 | 66 |
| Ejemplo A104 | 68 |
| Ejemplo A105 | 67 |
| Ejemplo A106 | 69 |
| Ejemplo A107 | 74 |
| Ejemplo A108 | 58 |
| Ejemplo A109 | 58 |
| Ejemplo A111 | 70 |
| Ejemplo A112 | 85 |
| Ejemplo A113 | 68 |
| Ejemplo A114 | 70 |
| Ejemplo A115 | 53 |
| Ejemplo A116 | 58 |
| Ejemplo A118 | 70 |
| Ejemplo A119 | 70 |
| Ejemplo A120 | 73 |
| Ejemplo A121 | 59 |
| Ejemplo A123 | 71 |

[Tabla 2-6]

Tabla 2 (continuación)

| compuesto de prueba | tasa inhibitoria (%) a 10 μM |
|---|---|
| Ejemplo A124 | 51 |

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| | |
|---|---|
| Ejemplo A125 | 69 |
| Ejemplo A126 | 68 |
| Ejemplo A127 | 71 |
| Ejemplo A128 | 83 |
| Ejemplo A129 | 82 |
| Ejemplo A130 | 76 |
| Ejemplo A131 | 87 |
| Ejemplo A132 | 83 |
| Ejemplo A133 | 80 |
| Ejemplo A134 | 82 |
| Ejemplo A135 | 76 |
| Ejemplo A136 | 62 |
| Ejemplo A137 | 75 |
| Ejemplo A138 | 85 |
| Ejemplo A139 | 76 |
| Ejemplo A140 | 83 |
| Ejemplo A141 | 86 |
| Ejemplo A142 | 87 |
| Ejemplo A143 | 75 |
| Ejemplo A144 | 82 |
| Ejemplo A145 | 76 |
| Ejemplo A146 | 77 |
| Ejemplo A147 | 99 |
| Ejemplo A148 | 94 |
| Ejemplo A149 | 69 |
| Ejemplo A150 | 81 |
| Ejemplo A151 | 78 |
| Ejemplo A152 | 76 |

1747

| | |
|---|---|
| Ejemplo A153 | 74 |
| Ejemplo A154 | 82 |
| Ejemplo A155 | 81 |
| Ejemplo A156 | 80 |
| Ejemplo A157 | 80 |
| Ejemplo A158 | 79 |
| Ejemplo A159 | 74 |
| Ejemplo A160 | 92 |

[Tabla 2-7]

Tabla 2 (continuación)

| compuesto de prueba | tasa inhibitoria (%) 10 μM |
|---|---|
| Ejemplo A161 | 84 |
| Ejemplo A162 | 79 |
| Ejemplo A163 | 87 |
| Ejemplo A164 | 85 |
| Ejemplo A165 | 85 |
| Ejemplo A166 | 75 |
| Ejemplo A167 | 86 |
| Ejemplo A168 | 90 |
| Ejemplo A169 | 86 |
| Ejemplo A170 | 89 |
| Ejemplo A171 | 86 |
| Ejemplo A172 | 82 |
| Ejemplo A173 | 74 |
| Ejemplo A174 | 98 |
| Ejemplo A175 | 68 |
| Ejemplo A176 | 96 |
| Ejemplo A177 | 90 |

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| | |
|---|---|
| Ejemplo A178 | 86 |
| Ejemplo A179 | 84 |
| Ejemplo A180 | 83 |
| Ejemplo A181 | 88 |
| Ejemplo A182 | 95 |
| Ejemplo A183 | 88 |
| Ejemplo A184 | 74 |
| Ejemplo A185 | 71 |
| Ejemplo A186 | 85 |
| Ejemplo A187 | 90 |
| Ejemplo A188 | 77 |
| Ejemplo A190 | 86 |
| Ejemplo A191 | 82 |
| Ejemplo A192 | 72 |
| Ejemplo A193 | 80 |
| Ejemplo A194 | 88 |
| Ejemplo A195 | 84 |
| Ejemplo A196 | 87 |
| Ejemplo A198 | 87 |
| Ejemplo A199 | 88 |

[Tabla 2-8]

Tabla 2 (continuación)

| compuesto de prueba | tasa inhibitoria (%) a 10 μM |
|---|---|
| Ejemplo A200 | 89 |
| Ejemplo A202 | 86 |
| Ejemplo A204 | 86 |
| Ejemplo A206 | 70 |
| Ejemplo A208 | 83 |

1748

| | |
|---|---|
| Ejemplo A209 | 90 |
| Ejemplo A211 | 70 |
| Ejemplo A213 | 70 |
| Ejemplo A214 | 75 |
| Ejemplo A215 | 72 |

Tal como se mencionó con anterioridad, se demostró que el compuesto de la presente invención tiene superior acción inhibitoria de fijación de glucagón.

Ejemplo Experimental 2: prueba de acción supresora para el incremento de glucosa sanguínea inducida por glucagón (rata)

Ratas SD con alimentación completa (machos, 7 a 9 semanas de edad) se dejaron en ayunas, se administró por vía oral 0,5% de suspensión de metilcelulosa que contiene un compuesto de prueba (10 mg/kg de peso corporal) (grupo de administración de compuesto, 5 ratas por grupo) o 0,5% de una suspensión de metilcelulosa (grupo sin administración de compuesto, 12 ratas por grupo) y 60 min después se administró glucagón (15 μg/kg de peso corporal, Novo Nordisk Pharma Ltd.) por vía subcutánea. A los 20 min de la administración de glucagón, se tomaron muestras de sangre de la vena de la cola de las ratas y se midió la glucosa sanguínea mediante un kit de automedición de glucosa ACCU-CHEK (Roche Diagnostics K.K.). Además, como grupo sin tratamiento (5 ratas por grupo), se midió la glucosa sanguínea de ratas (grupo sin compuesto de tratamiento) sin la administración de glucagón de la misma manera que le anterior.

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Se calculó la diferencia entre la glucosa sanguínea del grupo sin administración de compuesto o el grupo con administración de compuesto y la glucosa sanguínea del grupo sin tratamiento. El porcentaje de "la diferencia entre la glucosa sanguínea del grupo con administración de compuesto y la glucosa sanguínea del grupo sin tratamiento" en forma de "la tasa de incremento de glucosa sanguínea (% de control)" en donde "la diferencia entre la glucosa sanguínea del grupo sin administración de compuesto y del grupo sin tratamiento" es 100%. Los resultados se muestran en la Tabla 3.

Tabla 3

| Compuesto de prueba | dosis de administración de compuesto glucosa sanguínea (mg/kg) | tasa de incremento (% de control) |
|---|---|---|
| Ejemplo A41 | 10 | 16,6 |
| Ejemplo A53 | 10 | 27,4 |
| Ejemplo A73 | 10 | 24,2 |
| Ejemplo A78 | 10 | 26,3 |
| Ejemplo A83 | 10 | 43,0 |

Tal como se mencionó con anterioridad, se demostró que el compuesto de la presente invención tiene superior acción supresora del incremento de la glucosa sanguínea.

Ejemplo de formulación 1 (producción de cápsula)

1) compuesto de Ejemplo 1 30 mg
2) celulosa en polvo fino 10 mg
3) lactosa 19 mg

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4) estearato de magnesio 1 mg

Total 60 mg

1), 2), 3) y 4) se mezclan y se llenan en una cápsula de gelatina.

Ejemplo de formulación 2 (producción de comprimido)

1) compuesto de Ejemplo 1 30 g

2) lactosa 50 g

3) almidón de maíz 15 g

4) carboximetilcelulosa de calcio 44 g

5) estearato de magnesio 1 g

1000 comprimidos total 140 g

La cantidad total de 1), 2) y 3) y 30 g de 4) se amasa con agua, se seca en vacío y se tamiza. A este polvo tamizado se añaden 14 g de 4) y 1 g de 5) y la mezcla se comprime mediante una máquina para comprimidos. De esta manera, se obtienen 1000 comprimidos que contienen 30 mg de compuesto del Ejemplo 1 por comprimido.

Aplicabilidad industrial

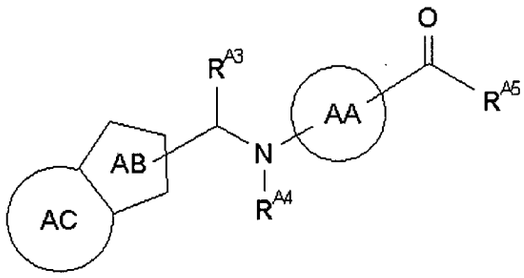
El compuesto de la presente invención tiene acción antagonista de glucagón y es útil para la profilaxis o el tratamiento de diabetes y similares.

La presente solicitud se basa en las solicitudes de patente N.° 2008-055250 y 2009-025511 presentadas en Japón, cuyos contenidos se incorporan en su totalidad en la presente para esta referencia.

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## REIVINDICACIONES

1. Un compuesto caracterizado por la siguiente fórmula:




(IA)

en donde el anillo AA es un anillo benceno opcionalmente sustituido o un heterociclo aromático de 5 ó 6 miembros opcionalmente sustituido;

el anillo AB es un heterociclo aromático de 5 miembros opcionalmente sustituido;

el anillo AC es un anillo benceno opcionalmente sustituido o un heterociclo aromático de 5 ó 6 miembros opcionalmente sustituido;

$R^{A3}$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, es un grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido, es un grupo arilo $C_{6-14}$ opcionalmente sustituido o un grupo heterocíclico opcionalmente sustituido;

$R^{A4}$ es un átomo de hidrógeno o un grupo alquilo $C_{1-6}$;

$R^{A5}$ es $-(CH_2)_3-COOR^{A11}$ o $-NR^{A6}-CR^{A7}R^{A8}-CR^{A9}R^{A10}-COOR^{A11}$;

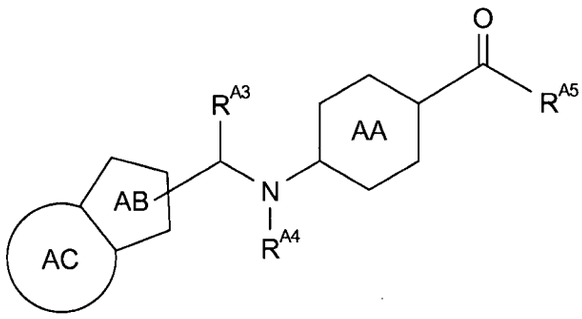
$R^{A6}$, $R^{A7}$, $R^{A8}$, $R^{A9}$ y $R^{A11}$ son cada uno, de modo independiente, un átomo de hidrógeno o un grupo alquilo $C_{1-6}$; y

$R^{A10}$ es un átomo de hidrógeno, un grupo alquilo $C_{1-6}$ o un grupo hidroxi,

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o una de sus sales.

2. El compuesto de acuerdo con la reivindicación 1, caracterizado porque la fórmula (IA) es la siguiente fórmula




(IA')

, y

el anillo AA es un anillo benceno o un heterociclo aromático de 6 miembros.

3. El compuesto de acuerdo con la reivindicación 2, caracterizado porque $R^{A3}$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, es un grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido o un grupo heterocíclico de 5 ó 6 miembros opcionalmente sustituido;

$R^{A4}$ es un átomo de hidrógeno;

$R^{A5}$ es $-(CH_2)_3-COOR^{A11}$ o $-NR^{A6}-(CH_2)_2-COOR^{A11}$;

$R^{A6}$ es un átomo de hidrógeno o metilo; y

$R^{A11}$ es un átomo de hidrógeno, metilo o etilo.

4. Ácido 3-{[(4-{[Ciclohexil(3-metil-1-benzofuran-2-il)metil]amino}fenil)carbonil](metil)amino}propanoico o una de sus sales.

5. Ácido 3-{[(6-{[Ciclohexil(5-fluoro-3-metil-1-benzofuran-2-il)metil]amino}piridin-3-il)carbonil](metil)amino}propanoico o una de sus sales.

6. Ácido 3-{[(4-{[2-Etil-1-(5-fluoro-3-metil-1-

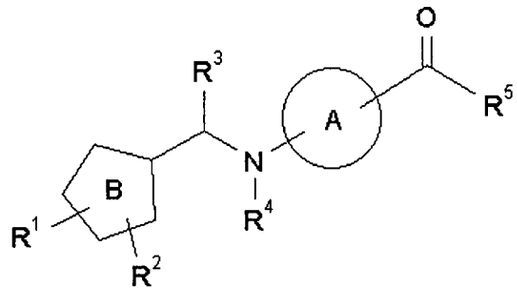
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benzofuran-2-
il)butil]amino}fenil)carbonil](metil)amino}propanoico o una de sus sales.

7. Ácido 3-[{[4-({1-[5-(ciclopropilmetoxi)-3-metil-1-benzofuran-2-il]-2-metilpropil}amino)fenil]carbonil}(metil)amino]propanoico o una de sus sales.

8. Ácido 3-[{[4-({ciclohexil[3-metil-5-(tetrahidro-2H-piran-4-iloxi)-1-benzofuran-2-il]metil}amino)fenil]carbonil}(metil)amino]propanoico o una de sus sales.

9. Un compuesto caracterizado por la siguiente fórmula:




(I)

en donde el anillo A es un anillo benceno opcionalmente sustituido o un heterociclo aromático de 5 ó 6 miembros opcionalmente sustituido;

el anillo B es pirazol;

$R^1$ y $R^2$ son cada uno, de modo independiente, un grupo hidrocarburo opcionalmente sustituido, un grupo heterocíclico opcionalmente sustituido, un grupo hidroxi opcionalmente sustituido o acilo;

$R^3$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, es un grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido, es un grupo

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arilo $C_{6-14}$ opcionalmente sustituido o un grupo heterocíclico opcionalmente sustituido;

$R^4$ es un átomo de hidrógeno o un grupo alquilo $C_{1-6}$;

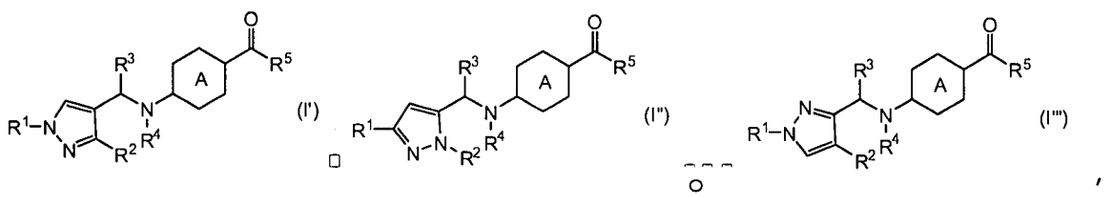
$R^5$ es $-(CH_2)_3-COOR^{11}$ o $-NR^6-CR^7R^8-CR^9R^{10}-COOR^{11}$;

$R^6$, $R^7$, $R^8$, $R^9$ y $R^{11}$ son cada uno, de modo independiente, un átomo de hidrógeno o un grupo alquilo $C_{1-6}$; y

$R^{10}$ es un átomo de hidrógeno, un grupo alquilo $C_{1-6}$ o un grupo hidroxi,

excluyendo N-[4-[[(1-fenil-5-propil-1H-pirazol-4-il)metil]amino]benzoil]-β-alanina o una de sus sales.

10. El compuesto de acuerdo con la reivindicación 9, caracterizado porque la fórmula (I) es la siguiente fórmula




y el anillo A es un anillo benceno o un heterociclo aromático de 6 miembros.

11. El compuesto de acuerdo con la reivindicación 9, caracterizado porque $R^1$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, es un grupo arilo $C_{6-14}$ opcionalmente sustituido o un grupo heterocíclico aromático de 5 ó 6 miembros opcionalmente sustituido;

$R^2$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, un grupo alcoxi $C_{1-6}$ opcionalmente sustituido o es un grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido;

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$R^3$ es un grupo alquilo $C_{1-6}$ opcionalmente sustituido, es un grupo cicloalquilo $C_{3-10}$ opcionalmente sustituido o un grupo heterocíclico de 5 ó 6 miembros opcionalmente sustituido;

$R^4$ es un átomo de hidrógeno;

$R^5$ es $-(CH_2)_3-COOR^{11}$ o $-NR^6-CH_2-CR^9R^{10}-COOR^{11}$;

$R^6$ es un átomo de hidrógeno o metilo;

$R^9$ es un átomo de hidrógeno, metilo o etilo;

$R^{10}$ es un átomo de hidrógeno, metilo o etilo; y

$R^{11}$ es un átomo de hidrógeno, metilo o etilo.

12. Ácido 3-[({4-[(ciclohexil{3-metil-1-[5-(trifluorometil)piridin-2-il]-1H-pirazol-4-il}metil)amino]fenil}carbonil)amino]propanoico o una de sus sales.

13. Ácido 3-[{[4-({ciclohexil[1-(3-metoxifenil)-3-metil-1H-pirazol-4-il]metil}amino)fenil]carbonil}(metil)amino]propanoico o una de sus sales.

14. Ácido 3-[{[4-({ciclohexil[1-(3-metoxifenil)-4-metil-1H-pirazol-3-il]metil}amino)fenil]carbonil}(metil)amino]propanoico o una de sus sales.

15. Un profármaco del compuesto de acuerdo con la reivindicación 1 u 9.

16. Un medicamento caracterizado porque comprende el compuesto de acuerdo con la reivindicación 1 o 9 o uno de sus profármacos.

17. El medicamento de acuerdo con la reivindicación 16 caracterizado porque es un antagonista de glucagón.

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18. El medicamento de acuerdo con la reivindicación 16 caracterizado porque es un agente supresor de la producción de azúcar.

19. El medicamento de acuerdo con la reivindicación 16 caracterizado porque es un agente para la terapia o el tratamiento de diabetes.

20. Un método para suprimir la producción de azúcar en un mamífero, caracterizado porque comprende la administración del compuesto de acuerdo con la reivindicación 1 o uno de sus profármacos o el compuesto de acuerdo con la reivindicación 9 o uno de sus profármacos al mamífero.

21. Un método para la profilaxis o el tratamiento de diabetes en un mamífero, caracterizado porque comprende la administración del compuesto de acuerdo con la reivindicación 1 o uno de sus profármacos o el compuesto de acuerdo con la reivindicación 9 o uno de sus profármacos al mamífero.

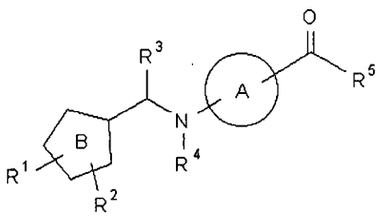
22. Uso del compuesto de acuerdo con la reivindicación 1 o uno de sus profármacos o el compuesto de acuerdo con la reivindicación 9 o uno de sus profármacos para la fabricación de un medicamento para suprimir la producción de azúcar.

23. Uso del compuesto de acuerdo con la reivindicación 1 o uno de sus profármacos o el compuesto de acuerdo con la reivindicación 9 o uno de sus profármacos para la producción de un agente para la terapia o el tratamiento de diabetes.

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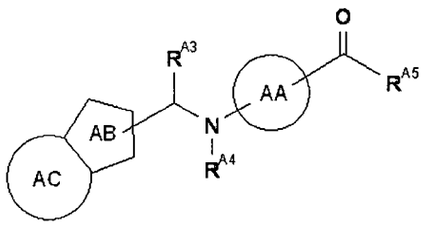
**RESUMEN**

Se describe un agente para la prevención y tratamiento de diabetes, el cual tiene excelentes efectos medicinales. Específicamente se describe un compuesto representado por la fórmula (I) o (IA) o una de sus sales.
(En las fórmulas, los símbolos se definen como en la descripción.)




(I)

o




(IA)

SEQUENCE LISTING

<110> Takeda Pharmaceutical Company Limited

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<130> 091369

<150> JP2008-055250
<151> 2008-03-05

<150> JP2009-025511
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1761

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2009/054095

A. CLASSIFICATION OF SUBJECT MATTER
See extra sheet.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D209/14, A61K31/343, A61K31/381, A61K31/404, A61K31/415, A61K31/416, A61K31/4184, A61K31/4355, A61K31/4365, A61K31/437, A61K31/4439, A61P3/10, A61P43/00, C07D231/12, C07D231/20, C07D231/56, C07D235/14, C07D307/81,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996 Jitsuyo Shinan Toroku Koho 1996-2009
Kokai Jitsuyo Shinan Koho 1971-2009 Toroku Jitsuyo Shinan Koho 1994-2009

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS/REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | JP 2006-500325 A (NOVO NORDISK A.S.), 05 January, 2006 (05.01.06), Claims & WO 2004/002480 A1 & US 2004/014789 A1 & US 6881746 B2 & US 2005/256175 A1 & EP 1519723 A1 | 1-19,22-23 |
| A | JP 2005-511683 A (NOVO NORDISK A.S.), 28 April, 2005 (28.04.05), Claims & WO 2003/048109 A1 & US 2003/236292 A1 & EP 1463715 A1 | 1-19,22-23 |
| A | WO 2007/106181 A2 (ELI LILLY & CO.), 20 September, 2007 (20.09.07), Claims & EP 1951661 A2 & US 2008/300308 A1 | 1-19,22-23 |

[X] 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 |
|---|---|
| 08 May, 2009 (08.05.09) | 19 May, 2009 (19.05.09) |
| Name and mailing address of the ISA/ Japanese Patent Office | Authorized officer |
| Facsimile No. | Telephone No. |

Form PCT/ISA/210 (second sheet) (April 2007)

1762

**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/JP2009/054095

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | JP 2006-528687 A (MERCK & CO., INC.),<br>21 December, 2006 (21.12.06),<br>Claims<br>& WO 2004/100875 A2 & EP 1626717 A2<br>& US 2007/093544 A1 | 1-19,22-23 |
| A | WO 2004/098528 A2 (BRISTOL-MYERS SQUIBB CO.),<br>18 November, 2004 (18.11.04),<br>Page 39, example 6<br>& US 2004/248853 A1 & EP 1620108 A2<br>& US 2006/247247 A1 & US 7151113 B2<br>& US 7253170 B2 & US 2008/004278 A1 | 9-16 |

1763

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2009/054095

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 20, 21
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 20 and 21 include the methods for treatment of the human body or animal body by surgery or therapy and thus relate to a subject matter which this International Searching Authority is not required, under the provisions of PCT Rule 67.1(iv) in conjunction with PCT Rule 43bis.1(b), to search.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

the

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

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**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/JP2009/054095

Continuation of A. CLASSIFICATION OF SUBJECT MATTER
(International Patent Classification (IPC))

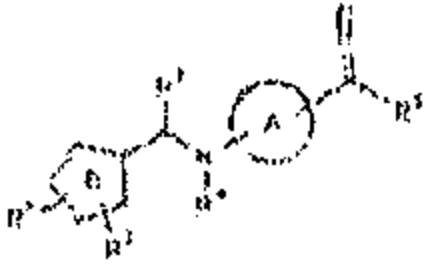
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(According to International Patent Classification (IPC) or to both national classification and IPC)

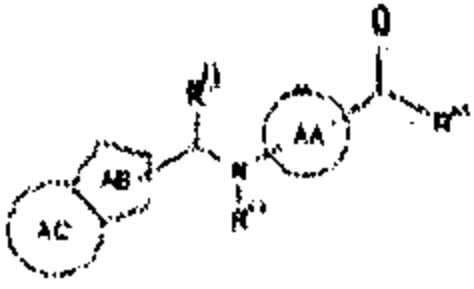
Continuation of B. FIELDS SEARCHED
Minimum documentation searched (International Patent Classification (IPC))

C07D333/58, C07D401/04, C07D471/04, C07D491/048, C07D495/04

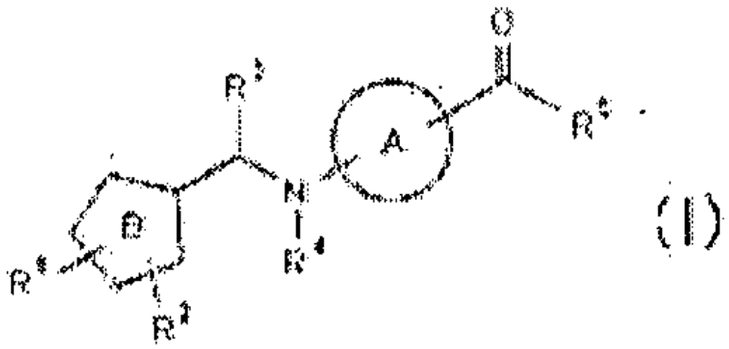
Minimum documentation searched (classification system followed by classification symbols)



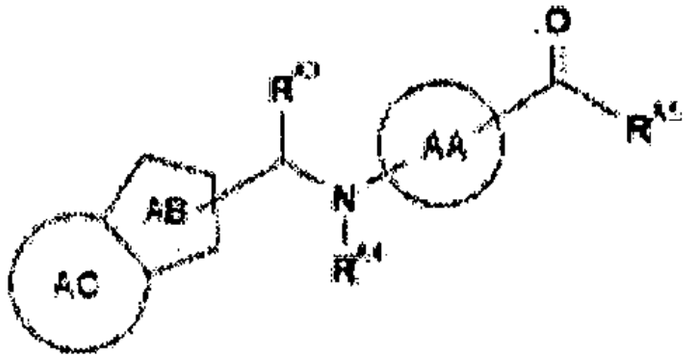
(I)



(IA)



(I)



(IA)

1767

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 10 - 78,550
FECHA : SEPTIEMBRE 20 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-122832- -00000-0000
Fecha: 2010-10-04 17:26:31 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1769

***** 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 | 156798832 | 20/09/2010 | 42,238,000.00 |

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

| CANT. | RENTISTICO | CONCEPTO | | TOTAL CONCEPTO |
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| 1 | 50005-01-09 OTROS SERVICIOS DE PROPIEDAD I | 99 | OTROS SERVCIOS ADMINISTRATIVOS | 20,000.00 |
| | | | TOTAL : $ | 20,000.00 |

SON: VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

OJO: 1656-841-063-4.

1768

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 80,736
FECHA : SEPTIEMBRE 27 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

**No. 10-122832- -00000-0000**

Fecha: 2010-10-04 17:26:31 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1769

***** 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 | 132664700 | 27/06/2010 | 57,040,000.00 |

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

| CANT. | RENTISTICO | CONCEPTO | TOTAL CONCEPTO |
|---|---|---|---|
| 1 | 50005-01-09 OTROS SERVICIOS DE PROPIEDAD I | *** TASA ANUAL AÑOS 9 a 12 CUATRENIO | 437,000.00 |

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TOTAL : $ 437,000.00

SON: CUATROCIENTOS TREINTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO: 546 56 - 841 - 063-4.

1769

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 80,737
FECHA : SEPTIEMBRE 27 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-122832- -00000-0000
Fecha: 2010-10-04 17:26:31 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1769

***** 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 | 132664700 | 27/06/2010 | 57,040,000.00 |

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

| CANT. | RENTISTICO | CONCEPTO | TOTAL CONCEPTO |
|---|---|---|---|
| 1 | 50005-01-09 OTROS SERVICIOS DE PROPIEDAD I | *** TASA ANUAL AÑOS 9 a 12 CUATRENIO | 437,000.00 |

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TOTAL : $ 437,000.00

SON: CUATROCIENTOS TREINTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO: 14656-841-063-4

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-122832- -00000-0000

Fecha: 2010-10-04 17:26:31 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1769

ES

**PATENTE DE INVENCIÓN** ☐ **MODELO DE UTILIDAD** ☐ **Art 33 Decisión 486/00**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

**PATENTE DE INVENCIÓN PCT** ☑ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

**DISEÑO INDUSTRIAL** ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

**ESQUEMA DE TRAZADO** ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
SUAREZ DE PAEZ LUZ CLEMENCIA
Apoderado(a) y/o Representante de
TAKEDA PHARMACEUTICAL COMPANY LIMITED

| | | |
|---|---|---|
| REFERENCIA | Radicación No. | 10 122832 |
| | Solicitud internacional | PCT/JP2009/054095 |
| | Fecha inicio fase nacional | 05/10/2010 |
| | Trámite | 11 |
| | Evento | 378 |
| | Actuación | 430 |
| | Oficio No. | № 14361 |

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 05 NOV. 2010
adpa11