Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 06-505/4

54. **TÍTULO** COMPUESTOS DE PIRIDINA COMO INHIBIDORES DE DIPEPTIDIL PEPTIDASA IV

51. **CLASIFICACIÓN INTERNACIONAL** C07D 213/80, 401/12, 413/06, 409/12 C07D 405/12, C07F 9/40, A61K 31/4402 A61P 3/10

71. **SOLICITANTE** TAKEDA PHARMACEUTICAL COMPANY LIMITED

DOMICILIO OSAKA, JAPÓN

74. **APODERADO** EMILIO FERRERO
C.C. 438.019 DE USAQUÉN.

22. **BOGOTÁ, D. C.,**

Publicación
[illegible]
Complementación radicada
[illegible]

(FORMA P-10)

CAVELIER ABOGADOS 050514 ID-83

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-050514- -00000-0000
Fec: 2006-05-25 16:51:57 Dep: 2000 NUEVAS CREACIONES
Tra: 11 PATENTES II
Cla: 375 FASE NACIONAL
Act 411 PRESENTACION Folios: 852

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

31-05-06

SOLICITUD DE:

(1) ☒ 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 5410045
Japón

Domicilio: Osaka 5410045
Japón

IDENTIFICACIÓN

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

(3) REPRESENTANTE O APODERADO

Nombre: EMILIO FERRERO
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@carnyp.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 438.019 T.P 31.929

(4) INVENTOR (ES) (72)

1. **Satoru OI**
c/o Takeda Pharmaceutical company Limited
17-85, jusohonmachi-2-chome
Yodogawa-ku, Osaka-shi
Osaka 532-8686
Japón

2. **Hironobu MAEZAKI**
c/o Takeda Pharmaceutical company Limited
17-85, jusohonmachi-2-chome
Yodogawa-ku, Osaka-shi
Osaka 532-8686
Japón

3. **Nobuhiro SUZUKI**
c/o Takeda Pharmaceutical company Limited
10, Wadai, Tsukuba-shi
Ibaraki 300-4293
Japón

(5) PCT (86)

Solicitud Internacional No. PCT/JP2004/016457 Fecha: 29 de octubre de 2004
Publicación Internacional No. WO 2005/042488 A1 Fecha: 12 de mayo de 2005

(6) Título (54)

COMPUESTOS DE PIRIDINA COMO INHIBIDORES DE DIPEPTIDIL PEPTIDASA IV

(7) Clasificación Internacional (51) C07D 213/80, 401/12, 413/06, C07F 9/40, C07D 409/12, 405/12, A61K 31/4402, A61P 3/10.

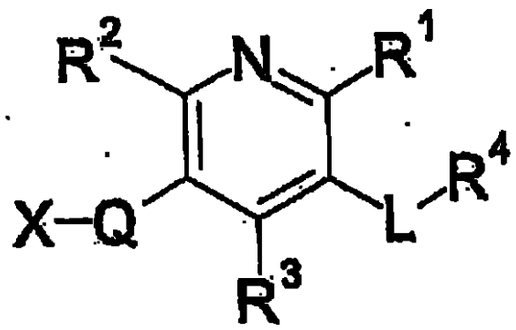
(8) Prioridad SI☒ NO☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	JP	31 de octubre de 2003	2003-373776
	JP	6 de febrero de 2004	2004-030491
	JP	3 de junio de 2004	2004-165977

(9) **Comprobante de pago No.:** 06-36.151 **Fecha:** 15 de mayo de 2006

(10) **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 483.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

(11) **FIGURA CARACTERÍSTICA**



(I)

12

NOMBRE: EMILIO FERRERO

FIRMA:

C.C. 438.019 de Usaquén T.P. 31.929

JDF

4

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2005/042488 A1
   Descripción:
2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.
3. ☒Extracto de publicación.

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a Nº 72-35
BOGOTA, 3 - 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

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

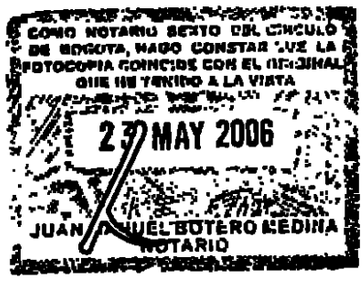
por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª Nº 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero 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 [illegible] shall suffice. If any of the appointees were to be definitively absent, the following [illegible] shall take his place. When the absence or the impediment of the principal representative, or of the first or second alternate, in their turn ceases, the representation can be taken again 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 alternate [illegible]

NOTARIO SESENTA Y SEIS DEL CIRCULO
FOTOCOPIA CONFORME CON EL ORIGINAL QUE TUVE A LA VISTA
27 NOV 2008
NOTARIO
REPUBLICA DE COLOMBIA

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 relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit


COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
23 MAY 2006
JUAN MANUEL BOTERO MEDINA
NOTARIO

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.

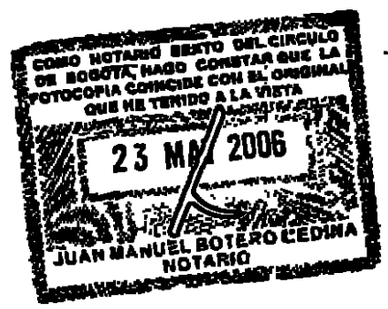
Dado y firmado hoy/Given and signed this 14th day of December, 2004

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 NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
23 MAY 2006
JUAN MANUEL BOTERO MEDINA
NOTARIO


COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
23 MAY 2006
JUAN MANUEL BOTERO LEDINA
NOTARIO

7

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

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
23 MAY 2006
JUAN MANUEL BOLAÑOS LEDINA
NOTARIO

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

8

大阪法務局所属　公証人役場

認証登簿　平成１６年 第　334　号

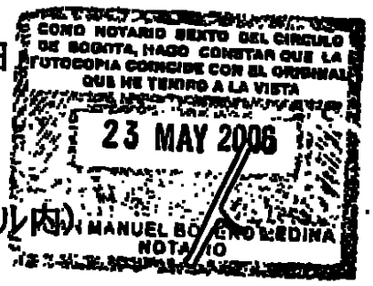
嘱託人 武田薬品工業株式会社 常務取締役　知的財産部長 秋元浩

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

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
23 MAY 2006
MANUEL BO[illegible] MEDINA
NOTARIO



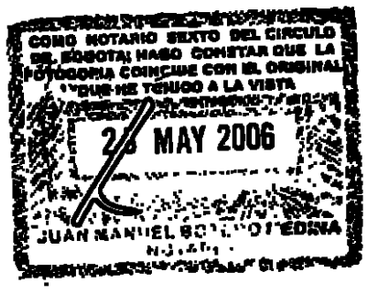
大阪市西区江戸堀１丁目１０番８号（帝人殖産ビル内）

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

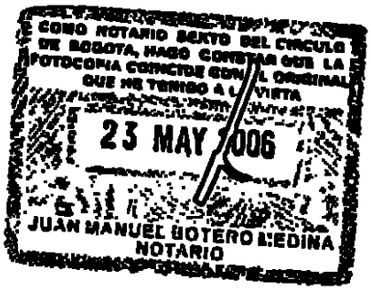
公証人 藤田清臣


COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA; HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
25 MAY 2006
JUAN MANUEL

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.

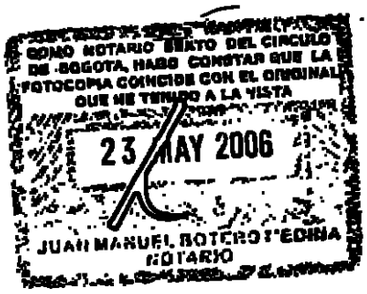
Dated this 14th day of December, 2004



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

Kiyoomi Fujita

Kiyoomi Fujita
Notary attached
to The Osaka Legal
Affairs Bureau


COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
23 MAY 2006
JUAN MANUEL ROTERO TEDRIA
NOTARIO

総第 3603 号

証　　明

大阪法務局所属公証人　藤田清臣

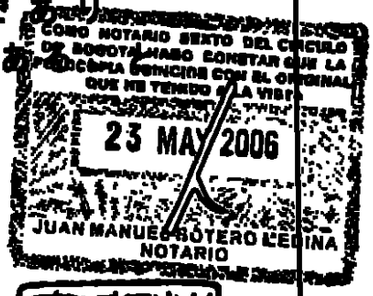
平成 16年12 月14 日付

平成16年 登知 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　梅津和恭



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

11

THE OSAKA CHAMBER OF COMMERCE & INDUSTRY

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

November 17, 2004

To whom it may concern:

CERTIFICATE OF MEMBERSHIP

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
23 MAY 2006
JUAN MANUEL BOTERO LEDUBA
NOTARIO

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

A №009149

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2005 FEB -4 A 2:33

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

27 MAY 2006

JUAN MANUEL BOTERO MEDINA
NOTARIO

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 los 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

Derechos: US$23.oo

RAFAEL RICARDO OROZCO
Segundo Secretario

OFICINA DE RELACIONES EXTERIORES
085749
LA FIRMA APARECE EN EL ANVERSO
RECONOCIDA ANTE LOS FUNCIONARIOS DESEMPEÑA

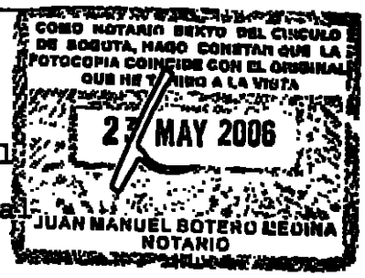
TRADUCCIÓN OFICIAL No. 02.04/05b realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia y registrado ante el Ministerio de Relaciones Exteriores de Colombia.

A continuación se traducen los sellos y legalizaciones de un documento por medio del cual **TAKEDA PHARMACEUTICAL COMPANY LIMITED** d miciliado 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 Propiedad Intelectual de Takeda Pharmaceutical Company Limited.

Expedido hoy 14 de diciembre de 2004

10-8, Edobori 1-chome

Nishi-ku, Osaka, Japón

Firma ilegible

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

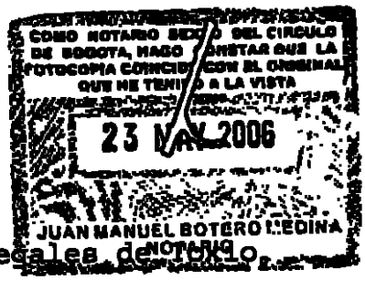
DOCUMENTO ANTERIOR EN JAPONÉS

(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 octubre 1961)

1. País: JAPÓN

   Este documento público

2. ha sido firmado por Kiyoomi FUJITA

3. actuando en calidad de Director de la Oficina de Asunt s Legales de Tokio

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

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 HONMACHIBASHI, CHUO-KU, OSAKA 540-0029, JAPÓN
FAX: (06) 6944-6248 TEL: 6944-6400 6411
URL: http://www.osaka.cci.or.jp/

Noviembre 17 de 2004

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
23 MAY 2005
JUAN MANUEL SOTERO ECHEVERRIA
NOTARIO

A quién pueda interesar:

CERTIFICADO DE MEMBRESÍA

El presente es para certificar que la siguiente compañía está registrada como miembro de esta Cámara.

Nombre de la compañía: Takeda Pharmaceutical 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

Númer de Membresía: KT-01-00080

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

COINCIDE(N) CON LA FIRMA REGISTRADA POR
EL (ELLOS) EN ESTA NOTARIA
SANTAFE DE BOGOTA, 08 FEB 2005

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

MINISTERIO DE
RELACIONES EXTERIORES

08 FEB -8 P 2:39

313391

JEFE DE LEGALIZACIONES
BOGOTA D.C.

LA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA

23 MAY 2006

JUAN MANUEL BOTERO MEDINA
NOTARIO

15

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.

COMO NOTARIO SEXTO DEL CIRCU... DE BOGOTA, HAGO CONSTAR QUE LA ... COINCIDE CON EL QUE ... QUE HE TENIDO A LA VISTA

23 MAY 2006

JUAN MANUEL ... NOTARIO

Es traducción fiel y completa de la cual se hizo copia en esta oficina para su confrontación.

DVZ/ID-6472/WPCL002G/COLO 14656-845-001-0

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)

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

SANTAFE DE BOGOTA, 08 FEB 2005

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2005 FEB -8 P 2:40

JEFE DE LEGALIZACIONES BOGOTA D.C.

MINISTERIO DE RELACIONES EXTERIORES

313395

CON LA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

23 MAY 2006

JUAN MANUEL BOTERO LEDINA
NOTARIO

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

CESION

Yo, (nosotros) abajo firmado (s)

1.
2.
3.

domiciliado(s) en

1.
2.
3.

declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención: COMPUESTOS DE PIRIDINA COMO INHIBIDORES DE DIPEPTIDIL-PEPTIDASA IV

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

Takeda Pharmaceutical Company Limited

constituida y existente de conformidad con las leyes de

Japon

domiciliada en 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0045 Japon

ASSIGNMENT

I (we), the undersigned

1. Satoru OI
2. Hironobu MAEZAKI
3. Nobuhiro SUZUKI

1. c/o Takeda Pharmaceutical Company Limited, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532-8686 Japan
2. same as 1 above
3. c/o Takeda Pharmaceutical Company Limited, 10, Wadai, Tsukuba-shi, Ibaraki 300-4293 Japan

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

PYRIDINE COMPOUNDS AS INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

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

Dado y firmado hoy/Given and signed this

____ day of _____ 200 6

en/in _____

Firma/Signature

Satoru Oi

1. Satoru OI

Hironobu Maezaki

2. Hironobu MAEZAKI

Nobuhiro Suzuki

3. Nobuhiro SUZUKI

大阪法務局所属　公証人役場

認証登簿　平成１８年 第　32　号

嘱託人　大井 悟、前﨑 博信 および 鈴木 伸宏 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　１８　年　２　月　２　日

大阪市西区江戸堀１丁目１０番８号（肥後橋ＴＳビル内）

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

公証人

REGISTER NUMBER 32 / 2006

I hereby certify that this document was signed before me and that the signatures appearing on the same are the true signatures of Messrs. Satoru OI, Hironobu MAEZAKI and Nobuhiro SUZUKI .

Dated this 2nd day of February, 2006

10-8, Edobori 1-chome,

Nishi-ku, Osaka, Japan.

Masaharu Kemma

Masaharu KEMMA

Notary attached

to The Osaka Legal

Affairs Bureau

総 第 320 号

証 明

大阪法務局所属公証人 見 満 正 治

平成 18年 2月 2日付

平成18年 登簿 第 32 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18年2月2日

平成 年 月 日

大阪法務局長 梅 津 和

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 06. 2. 2

Director of the Osaka Legal Affairs Bureau

20

TRADUCCIÓN OFICIAL 104/2006 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL, REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL APROBADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 POR EL MINISTERIO DE JUSTICIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE LA REPÚBLICA DE COLOMBIA Y MEDIANTE EL CUAL 1. SATORU OI; 2. HIRONOBU MAEZAKI Y 3. NOBUHIRO SUZUKI, DOMICILIADOS RESPECTIVAMENTE EN 1. C/O TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85, JUSOHONMACHI 2-CHOME, YODOGAWA-KU, OSAKA-SHI, OSAKA 5328686 JAPÓN; 2. LA MISMA ANTERIOR Y 3. C/O TAKEDA PHARMACEUTICAL COMPANY LIMITED, 10, WADAI, TSUKUBA-SHI, IBARAKI 300-4293, JAPÓN, DECLARAN POR EL PRESENTE SER LOS INVENTORES ÚNICOS Y VERDADEROS DEL INVENTO **COMPUESTOS DE PIRIDINA COMO INHIBIDORES DE DIPEPTIDIL PEPTIDASA IV** Y QUE CEDEN DICHA INVENCIÓN A TAKEDA PHARMACEUTICAL COMPANY LIMITED, EMPRESA ORGANIZADA Y EXISTENTE BAJO LAS LEYES DE JAPÓN, EMPRESA CONSTITUIDA Y EXISTENTE DE CONFORMIDAD CON LAS LEYES DE JAPÓN Y DOMICILIADA EN 1-1. DOSHOMACHI 4-CHOME, CHUO-KU, OSAKA-SHI, OSAKA 541-0045, JAPÓN JUNTO CON TODOS LOS DERECHOS INHERENTES Y QUE DICHA COMPAÑÍA QUEDA FACULTADA PARA SOLICITAR EN SU NOMBRE LA PATENTE CORRESPONDIENTE EN LA REPÚBLICA DE COLOMBIA.

DADO Y FIRMADO HOY (DATO EN BLANCO) DE 2006.

FIRMADO 1. SATORI OI, 2. HIRONOBU MAEZAKI Y 3. NOBUHIRO SUZUKI.

REGISTRO NÚMERO 32/2006

Por el 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 Satoru OI, Hironobu MAEZAKI y Nobuhiro SUZUKI. Fechado hoy 2 de febrero de 2006

10-8, Edobori 1-chome,
Nishiku, Osaka, Japón
Firmado: Masaharu KEMMA,
Notario adjunto la Oficina de Asuntos jurídicos de Osaka.

CERTIFICACIÓN

Por la presente certific que el certificado n tarial adjunto ha sido firmado por un notario debidamente aut rizad y practicante en Osaka, y que el sello oficial fijado sobre el mismo es genuino. Fecha 06, 2, 2006

Director de la Oficina de asuntos jurídicos de Osaka.

APOSTILLA:

(Convención de La Haya del 5 de octubre de 1961)

1. 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 de MASAHRU KEMMA, NOTARIO PÚBLICO,

CERTIFICADO

5. en OSAKA

6. el 2 de febrero de 2006.

7. por el Ministerio de Asuntos Exteriores

8. Número 0375

9. Sello: (ilegible)

10. Firma: TSUTOMU HIGUCHI

A nombre del Ministro de Asuntos Exteriores.

COLO-14656-841-009-7

WPCL002G. ID 7711

Bogotá, 24 de abril de 2006.

Eduardo Calado R.

Eduardo Calado Regnero
TRADUCTOR OFICIAL
INGLÉS - ESPAÑOL
Res. 541. Febrero de 1994

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

[illegible]

[illegible] CON LA FIRMA REGISTRADA POR [illegible] EN ESTA NOTARIA

SANTAFE DE BOGOTA, 24 ABR 2006

REPUBLICA DE COLOMBIA
SANTAFE DE BOGOTA D.C.

CO SE ABRE
RESPONSABILIDAD DEL TEXTO

ABR 24 P 12:59

[illegible]

MINISTERIO DE
RELACIONES EXTERIORES

437280

Eduardo Calado

CUYA FIRMA APARECE EN EL
ANCIPIENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

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PCT/JP2004/016457

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2004-030491	6 February 2004 (06.02.2004)	JP
2004-165977	3 June 2004 (03.06.2004)	JP

(71) Applicant *(for all designated States except US)*: TAKEDA PHARMACEUTICAL COMPANY LIMITED [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 5410045 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: OI, Satoru [JP/JP]; 7-10-509, Ayameikeminami 1-chome, Nara-shi, Nara 6310033 (JP). MAEZAKI, Hironobu [JP/JP]; 6-7-206, Honmachi 5-chome, Toyonaka-shi, Osaka 5600021 (JP). SUZUKI, Nobuhiro [JP/JP]; 16-61, Mino 4-chome, Mino-shi, Osaka 5620001 (JP).

(74) Agent: TAKASHIMA, Hajime; Fujimura Yamato Seimei Bldg., 2-14, Fushimimachi 4-chome, Chuo-ku, Osaka-shi, Osaka 5410044 (JP).

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

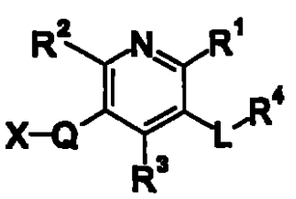
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/042488 A1

(54) Title: PYRIDINE COMPOUNDS AS INHIBITORS OF DIPEPTIDYL PEPTIDASE IV



(I)

(57) Abstract: A compound represented by the formula wherein R^1 and R^2 are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted hydroxy group; R^3 is an optionally substituted aromatic group; R^4 is an optionally substituted amino group; L is a divalent chain hydrocarbon group; Q is a bond or a divalent chain hydrocarbon group; and X is a hydrogen atom, a cyano group, a nitro group, an acyl group, a substituted hydroxy group, an optionally substituted thiol group, an optionally substituted amino group or an optionally substituted cyclic group; provided that when X is an ethoxycarbonyl group, then Q is a divalent chain hydrocarbon group. The compound has a peptidase inhibitory action, is useful as an agent for the prophylaxis or treatment of diabetes and the like, and is superior in efficacy, duration of action, specificity, lower toxicity and the like.

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Description

PYRIDINE COMPOUNDS AS INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

Technical Field

The present invention relates to a pyridine compound having a peptidase inhibitory activity, which is useful as an agent for the prophylaxis or treatment of diabetes and the like.

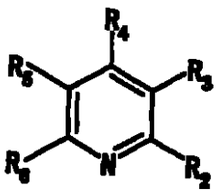
Background Art

Peptidase is known to relate to various diseases. Dipeptidyl dipeptidase-IV (hereinafter sometimes to be abbreviated as DPP-IV), which is one kind of peptidases, is serine protease that specifically binds with a peptide containing proline (or alanine) at the 2nd from the N-terminal and cleaves the C-terminal side of the proline (or alanine) to produce dipeptide. DPP-IV has been shown to be the same molecule as CD26, and reported to be also involved in the immune system. While the role of DPP-IV in mammals has not been entirely clarified, it is considered to play an important role in the metabolism of neuropeptides, activation of T cells, adhesion of cancerous cells to endothelial cells, invasion of HIV into cells and the like. Particularly, from the aspect of glycometabolism, DPP-IV is involved in the inactivation of GLP-1 (glucagon-like peptide-1) and GIP (Gastric inhibitory peptide/Glucose-dependent insulinotropic peptide), which are incretins. With regard to GLP-1, moreover, it is known that the physiological activity of GLP-1 is markedly impaired because it has a short plasma half-life of 1-2 minutes, and GLP-1(9-36)amide, which is a degradation product by DPP-IV, acts on GLP-1 receptor as an antagonist, thus decomposing GLP-1 by DPP-IV. It is also known that suppression of degradation of GLP-1 by inhibiting DPP-IV activity leads to potentiation of physiological activity that GLP-1 shows, such as glucose concentration-dependent insulin secretagogue effect and the like. From these facts, a compound having a DPP-IV inhibitory

activity is expected to show effect on impaired glucose tolerance, postprandial hyperglycemia and fasting hyperglycemia observed in type I and type II diabetes and the like, obesity or diabetic complications associated therewith and the like.

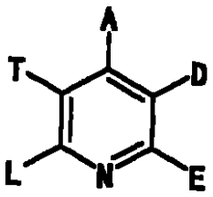
As pyridine compound, the following compounds have been reported.

(1) A compound represented by the formula



wherein R_2 and R_6 are each independently hydrogen, hydroxy, alkyl and the like; R_3 is hydroxy, amido and the like; R_4 is hydrogen, hydroxy, halogen and the like; and R_5 is hydrogen, hydroxy, halogen and the like, which has a cholesterol·ester · transfer · protein (hereinafter to be abbreviated as CETP) inhibitory action (see WO99/41237).

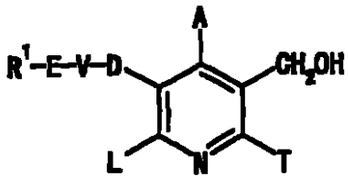
(2) A compound represented by the formula



wherein A is C_{6-10} aryl optionally substituted by halogen and the like; D is straigh-chain or branched alkyl having 8 or less carbon atoms optionally substituted by hydroxy; E and L are the same or different and each is straigh-chain or branched alkyl having 8 or less carbon atoms optionally substituted by C_{3-8} cycloalkyl, and the like; T is R^7-X- or R^8-(R^9)(R^{10})C- (wherein R^7 and R^8 are the same or different and each is C_{3-8} cycloalkyl, C_{6-10} aryl and the like; R^9 is hydrogen and the like; R^{10} is hydrogen, halogen, azido and the like), which has a CETP inhibitory action or a glucagon antagonistic action;

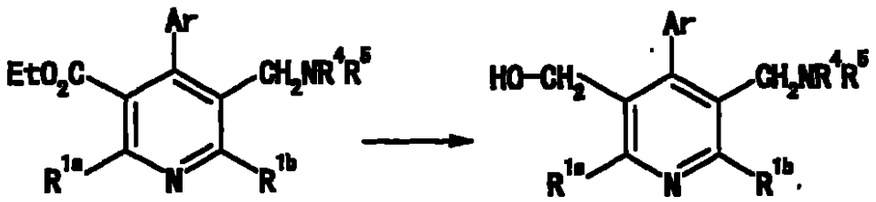
29

a compound represented by the formula



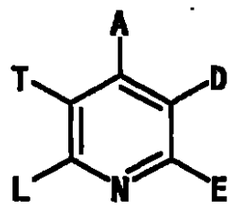
wherein A is C_{6-10} aryl optionally substituted by halogen and the like; D and E are the same or different and each is straigh-chain or branched alkyl having 8 or less carbon atoms optionally substituted by hydroxy; V is O, S or NR^5 (wherein R^5 is hydrogen, straigh-chain or branched alkyl having 6 or less carbon atoms, or phenyl); R^1 is C_{3-6} cycloalkyl, C_{6-10} aryl and the like; L and T are the same or different and each is trifluoromethyl and the like; and

a compound represented by the formula



wherein Ar is optionally substituted aromatic or heteroaromatic group; R^4 and R^5 are independently hydrogen, C_{1-6} alkyl and the like; R^{1a} and R^{1b} are independently trifluoromethyl, C_{1-6} alkyl and the like (see WO98/04528, US Patent No. 6218431).

(3) A compound represented by the formula

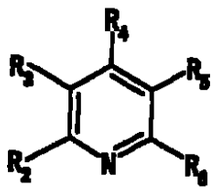


wherein A and E are the same or different and each is C_{6-10} aryl optionally substituted by halogen and the like; D is

straigh-chain or branched alkyl having 8 or less carbon atoms optionally substituted by hydroxy; L is C_{3-8} cycloalkyl, straigh-chain or branched alkyl having 8 or less carbon atoms, and the like; T is R^3-X- or R^4-(R^5)(R^6)C- (wherein R^3 and R^4 are the same or different and each is C_{3-8} cycloalkyl, C_{6-10} aryl and the like; R^5 is hydrogen and the like; R^6 is hydrogen, halogen, azido and the like), or a salt thereof, having a CETP inhibitory action

(see US Patent No. 5925645).

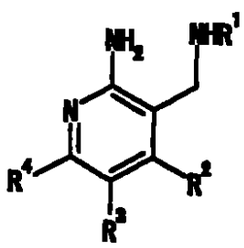
(4) A compound represented by the formula



wherein R_2 and R_6 are independent bromoalkyl, chloroalkyl and the like; R_4 is alkyl, cycloalkylalkyl, alkylthioalkyl, cycloalkyl, alkoxyalkyl or dialkylaminoalkyl; the one of R_3 and R_5 is CO-Y (wherein Y is alkylthio, alkoxy or N-containing heterocyclic group), the other is -(-C(R^9)(R^{10})-)n-X (wherein n is an integer of 1-3; R^9 and R^{10} are independently hydrogen, alkyl and the like; X is halogen, OH and the like) and the like, or a salt thereof, which has a herbicide action

(see WO92/20659).

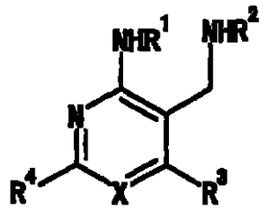
(5) A compound represented by the formula



wherein R^1 is hydrogen or lower alkyl; R^2 is heterocyclic group or aryl each optionally substituted by lower alkyl and the like; R^3 and R^4 may f rm a phenyl ring and the like each

optionally substituted by halogen and the like, together with the carbon atoms bonded thereto, or a salt thereof, which has a DPP-IV inhibitory action
(see WO03/068748).

(6) A compound represented by the formula



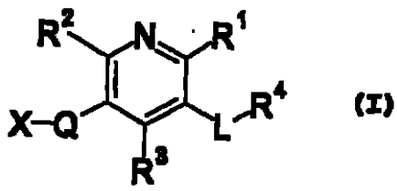
wherein X is N or CR^5 (wherein R^5 is hydrogen or lower alkyl); R^1 and R^2 are independently hydrogen or lower alkyl; R^3 is heterocyclic group or aryl each optionally substituted by lower alkyl and the like; R^4 is lower alkyl and the like, or a salt thereof, which has a DPP-IV inhibitory action
(see WO03/068757).

However, there is no report on the compound of the present invention.

Disclosure Of The Invention

There is a demand for the development of a compound having a peptidase inhibitory action, which is useful as an agent for the prophylaxis or treatment of diabetes and the like and superior in efficacy, duration of action, specificity, lower toxicity and the like.

The present inventors have first found that a compound represented by the formula



(I)

wherein

R^1 and R^2 are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted

hydroxy group;

R^3 is an optionally substituted aromatic group;

R^4 is an optionally substituted amino group;

L is a divalent chain hydrocarbon group;

Q is a bond or a divalent chain hydrocarbon group; and

X is a hydrogen atom, a cyano group, a nitro group, an acyl group, a substituted hydroxy group, an optionally substituted thiol group, an optionally substituted amino group or an optionally substituted cyclic group;

provided that

when X is an ethoxycarbonyl group, then Q is a divalent chain hydrocarbon group, and that the compound is not 2,6-diisopropyl-3-methylaminomethyl-4-(4-fluorophenyl)-5-pentylpyridine;

2,6-diisopropyl-3-aminomethyl-4-(4-fluorophenyl)-5-pentylpyridine;

2,6-diisopropyl-3-(dimethylamino)methyl-4-(4-fluorophenyl)-5-pentylpyridine;

2,6-diisopropyl-3-(ethylamino)methyl-4-(4-fluorophenyl)-5-pentylpyridine; and

3-(tert-butyldimethylsilyloxymethyl)-2,6-diisopropyl-4-(4-fluorophenyl)-5-(indolyl-5-aminomethyl)pyridine,

or a salt thereof

[hereinafter sometimes to be abbreviated as compound (I)], which is characterized by a chemical structure wherein an optionally substituted amino group is bonded to the 3-position of pyridine ring via a divalent chain hydrocarbon group and an optionally substituted aromatic group is bonded to the 4-position, has a superior peptidase inhibitory action and is useful as an agent for the prophylaxis or treatment of diabetes and the like. Based on this finding, the present inventors have conducted intensive studies and completed the present invention.

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Accordingly, the present invention relates to

1) compound (I);

2) compound (I), wherein R^1 and R^2 are the same or different and each is an optionally substituted hydrocarbon group, and X is a cyano group, a nitro group, an acyl group, a substituted hydroxy group, an optionally substituted thiol group or an optionally substituted cyclic group;

3) compound (I), wherein the acyl group for X is a carboxyl group;

4) compound (I), wherein R^1 and R^2 are the same or different and each is a C_{1-10} alkyl group optionally substituted by 1 to 3 substituent(s) selected from a C_{3-10} cycloalkyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkoxy group;

5) compound (I), wherein R^3 is a C_{6-14} aryl group optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atom(s) and a halogen atom;

6) compound (I), wherein R^4 is an amino group;

7) compound (I), wherein L is a C_{1-10} alkylene group;

8) compound (I), wherein Q is a bond;

9) compound (I), wherein X is an acyl group, a substituted hydroxy group, an optionally substituted thiol group or an optionally substituted amino group;

10) compound (I), wherein X is a carboxyl group;

11) compound (I), which is 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid;

5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid;

methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate;

{[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(2-morpholin-4-yl-2-oxoethyl)pyridin-3-yl]methyl}amine;

methyl 3-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-

methylphenyl)pyridin-3-yl]acetyl}amino)benzoate;
N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]isoxazole-4-carboxamide,
or a salt thereof;

12) a prodrug of compound (I);

13) a pharmaceutical agent comprising compound (I) or a prodrug thereof;

14) the pharmaceutical agent of 13) above, which is an agent for the prophylaxis or treatment of diabetes, diabetic complications, impaired glucose tolerance or obesity;

15) a peptidase inhibitor comprising compound (I) or a prodrug thereof;

16) the inhibitor of 15) above, wherein the peptidase is dipeptidyl dipeptidase-IV;

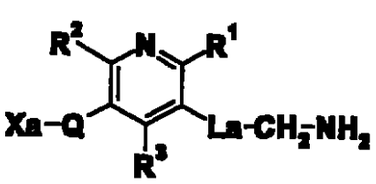
17) use of compound (I) or a prodrug thereof for the production of an agent for the prophylaxis or treatment of diabetes, diabetic complications, impaired glucose tolerance or obesity;

18) use of compound (I) or a prodrug thereof for the production of a peptidase inhibitor;

19) a method for the prophylaxis or treatment of diabetes, diabetic complications, impaired glucose tolerance or obesity in a mammal, which comprises administering compound (I) or a prodrug thereof to the mammal;

20) a method of inhibiting peptidase in a mammal, which comprises administering compound (I) or a prodrug thereof to the mammal;

21) a production method of a compound represented by the formula



(I-a)

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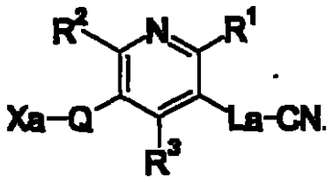
wherein

R^1, R^2, R^3 and Q are as defined in compound (I);

La is a bond or a divalent chain hydrocarbon group; and

Xa is a hydrogen atom, a nitro group, an acyl group, a substituted hydroxy group, an optionally substituted thiol group, an optionally substituted amino group or an optionally substituted cyclic group;

or a salt thereof, which comprises subjecting a compound represented by the formula



(II)

wherein each symbol is as defined above, or a salt thereof to a reduction reaction; and the like.

The compound of the present invention has a superior peptidase inhibitory action and is useful as an agent for the prophylaxis or treatment of diabetes and the like.

Best Mode For Carrying Out The Invention

Each symbol in the formula (I) is described in detail in the following.

As the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for R^1 or R^2, for example, a C_{1-10} alkyl group, a C_{2-10} alkenyl group, a C_{2-10} alkynyl group, a C_{3-10} cycloalkyl group, a C_{3-10} cycloalkenyl group, a C_{4-10} cycloalkadienyl group, a C_{6-14} aryl group, a C_{7-13} aralkyl group, a C_{8-13} arylalkenyl group, a C_{3-10} cycloalkyl-C_{1-6} alkyl group and the like can be mentioned.

As the C_{1-10} alkyl group here, for example, 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 can be mentioned.

As the C_{2-10} alkenyl group, for example, 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 can be mentioned.

As the C_{2-10} alkynyl group, for example, 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 can be mentioned.

As the C_{3-10} cycloalkyl group, for example, 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, bycyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[4.3.1]decyl and the like can be mentioned.

As the C_{3-10} cycloalkenyl group, for example, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl and the like can be mentioned.

As the C_{4-10} cycloalkadienyl group, for example, 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl and the like can be mentioned.

As the C_{6-14} aryl group, for example, phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl, biphenylyl and the like can be mentioned. Of these, phenyl, 1-naphthyl, 2-naphthyl and the like are preferable.

As the C_{7-13} aralkyl group, for example, benzyl, phenethyl, naphthylmethyl, biphenylylmethyl and the like can be mentioned.

As the C_{8-13} arylalkenyl group, for example, styryl and the like can be mentioned.

As the C_{3-10} cycloalkyl-C_{1-6} alkyl group, for example, cyclohexylmethyl and the like can be mentioned.

The aforementioned C_{1-10} alkyl group, C_{2-10} alkenyl group and C_{2-10} alkynyl group optionally have 1 to 3 substituent(s) at substitutable position(s).

As these substituents, for example,

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

(2) a C_{6-14} aryl group (e.g., phenyl, naphthyl);

(3) an aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, oxazolyl, thiazolyl, tetrazolyl, oxadiazolyl, pyrazinyl, quinolyl, indolyl) optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a carbamoyl group, a thiocarbamoyl group and a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl);

(4) a non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidinyl, piperazinyl, oxodioxolyl, oxodioxolanyl, oxo-2-benzofuranyl, oxooxadiazolyl) optionally substituted by a C_{1-6} alkyl group (e.g., methyl, ethyl);

(5) an amino group optionally mono- or di-substituted by substituent(s) selected from a C_{1-6} alkyl group (e.g., methyl, ethyl), a C_{1-6} alkyl-carbonyl group (e.g., acetyl, isobutanoyl, isopentanoyl) and a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl);

(6) a C_{1-6} alkylsulfonylamino group (e.g., methylsulfonylamino);

(7) an amidino group;

(8) a C_{1-6} alkyl-carbonyl group (e.g., acetyl, isobutanoyl, isopentanoyl);

(9) a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl,

ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl);

(10) a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl);

(11) a carbamoyl group optionally mono- or di-substituted by a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);

(12) a thiocarbamoyl group optionally mono- or di-substituted by a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);

(13) a sulfamoyl group optionally mono- or di-substituted by a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);

(14) a carboxyl group;

(15) a hydroxy group;

(16) a C_{1-6} alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);

(17) a C_{2-6} alkenyloxy group (e.g., ethenyloxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);

(18) a C_{3-10} cycloalkyloxy group (e.g., cyclohexyloxy);

(19) a C_{7-13} aralkyloxy group (e.g., benzyloxy);

(20) a C_{6-14} aryloxy group (e.g., phenyloxy, naphthyloxy);

(21) a C_{1-6} alkyl-carbonyloxy group (e.g., acetyloxy, tert-butylcarbonyloxy);

(22) a thiol group;

(23) a C_{1-6} alkylthio group (e.g., methylthio, ethylthio) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);

(24) a C_{7-13} aralkylthio group (e.g., benzylthio);

(25) a C_{6-14} arylthio group (e.g., phenylthio, naphthylthio);

(26) a sulfo group;

(27) a cyano group;

(28) a azido group;

(29) a nitro group;

(30) a nitroso group;

(31) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);

(32) a C_{1-6} alkylsulfinyl group (e.g., methylsulfinyl);

and the like can be mentioned.

The C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group, C_{4-10} cycloalkadienyl group, C_{6-14} aryl group, C_{7-13} aralkyl group, C_{8-13} arylalkenyl group and C_{3-10} cycloalkyl-C_{1-6} alkyl group, which are exemplarily recited for the aforementioned "hydrocarbon group", optionally have 1 to 3 substituent(s) at substitutable position(s).

As these substituents, for example,

those exemplarily recited for the substituents for the aforementioned C_{1-10} alkyl group and the like;

a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a carboxyl group, a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl) and a carbamoyl group;

a C_{2-6} alkenyl group (e.g., ethenyl, 1-propenyl) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a carboxyl group, a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl) and a carbamoyl group;

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

and the like can be mentioned.

The "hydrocarbon group" of the "optionally substituted hydrocarbon group" for R^1 or R^2 is preferably a C_{1-10} alkyl group, a C_{6-14} aryl group or a C_{7-13} aralkyl group, more preferably a C_{1-10} alkyl group.

The "optionally substituted hydrocarbon group" for R^1 or

R^2 is preferably

(1) a C_{1-10} alkyl group optionally substituted by 1 to 3 substituent(s) selected from a C_{3-10} cycloalkyl group, a C_{1-6} alkoxy-carbonyl group, a C_{1-6} alkoxy group and the like;

(2) a C_{6-14} aryl group optionally substituted by 1 to 3 substituent(s) selected from a halogen atom, a carboxyl group, a C_{1-6} alkoxy-carbonyl group, a carbamoyl group and the like; or

(3) a C_{7-13} aralkyl group.

Of these, a C_{1-10} alkyl group optionally substituted by 1 to 3 substituent(s) selected from a C_{3-10} cycloalkyl group, a C_{1-6} alkoxy-carbonyl group, a C_{1-6} alkoxy group and the like, is preferable.

As the "substituted hydroxy group" of the "optionally substituted hydroxy group" for R^1 or R^2, those exemplarily recited for X below can be used.

R^1 and R^2 are each preferably an "optionally substituted hydrocarbon group", more preferably a C_{1-10} alkyl group optionally substituted by 1 to 3 substituent(s) selected from a C_{3-10} cycloalkyl group, a C_{1-6} alkoxy-carbonyl group, a C_{1-6} alkoxy group and the like.

As the "aromatic group" of the "optionally substituted aromatic group" for R^3, for example, an aromatic hydrocarbon group, an aromatic heterocyclic group and the like can be mentioned.

As the aromatic hydrocarbon group, for example, a C_{6-14} aryl group which is exemplarily recited for the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for the aforementioned R^1 or R^2, and the like can be mentioned.

As the aromatic heterocyclic group, for example, a 5- to 7-membered monocyclic aromatic heterocyclic group containing 1 to 4 heteroatom(s) selected from an oxygen atom, a sulfur atom and a nitrogen atom as a ring-constituting atom, besides carbon atoms, and fused aromatic heterocyclic group can be mentioned.

As the fused aromatic heterocyclic group, for example, a group wherein these 5- to 7- membered monocyclic aromatic heterocyclic groups and a 6-membered ring containing 1 or 2 nitrogen atom(s), a benzene ring or a 5-membered ring containing one sulfur atom are fused, and the like can be mentioned.

As preferable examples of the aromatic heterocyclic group,

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, 6-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, oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), 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) and the like;

fused aromatic heterocyclic groups such as quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl), benzofuryl (e.g., 2-benzofuryl, 3-benzofuryl), benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-1-yl, benzimidazol-2-yl), indolyl (e.g., indol-1-yl, indol-3-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), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl) and the like,
and the like can be mentioned.

The "aromatic group" of the "optionally substituted aromatic group" for R^3 is preferably an aromatic hydrocarbon group, more preferably a C_{6-14} aryl group, still more preferably phenyl.

The "aromatic group" of the "optionally substituted aromatic group" for R^3 optionally has 1 to 3 substituent(s) at substitutable position(s).

As these substituents, for example, those exemplarily recited for the substituents for the C_{3-10} cycloalkyl group exemplarily recited for the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for the aforementioned R^1 or R^2 can be mentioned.

The substituents are preferably
a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);
a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
a C_{1-6} alkoxy-carbonyl group;
a carboxyl group;
a hydroxy group;
a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atom(s);
and the like, more preferably
a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);
a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
and the like.

The "optionally substituted aromatic group" for R^3 is preferably a C_{6-14} aryl group (wherein the C_{6-14} aryl group is preferably a phenyl) optionally substituted by 1 to 3

substituent(s) selected from a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a halogen atom (e.g., fluorine, chlorine, bromine, iodine), and the like.

As the "optionally substituted amino group" for R^4, for example, an amino group optionally substituted by 1 or 2 substituent(s) selected from a C_{1-10} alkyl group, a C_{2-10} alkenyl group, a C_{3-10} cycloalkyl group, a C_{3-10} cycloalkenyl group, a C_{6-14} aryl group, a C_{7-13} aralkyl group and a C_{8-13} arylalkenyl group, each of which is optionally substituted; an acyl group and the like can be mentioned.

As the C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group, C_{6-14} aryl group, C_{7-13} aralkyl group and C_{8-13} arylalkenyl group here, those exemplarily recited for the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for the aforementioned R^1 or R^2 can be used.

These C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group, C_{6-14} aryl group, C_{7-13} aralkyl group and C_{8-13} arylalkenyl group each optionally have 1 to 3 substituent(s) at substitutable position(s). As these substituents, for example,

a halogen atom (e.g., fluorine, chlorine, bromine, iodine);

a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl);

a C_{1-6} alkyl-carbonyl group;

a cyano group;

a carbamoyl group optionally mono- or di-substituted by a C_{1-10} alkyl group (e.g., methyl, ethyl, propyl, isopropyl, neopentyl);

a hydroxy group;

a carboxyl group;

and the like can be mentioned.

As the acyl group exemplarily recited for the

substituent of the "optionally substituted amino group", those exemplarily recited for X below can be used. Of these,

(1) a C_{1-6} alkyl-carbonyl group (e.g., acetyl, isobutanoyl, isopentanoyl);

(2) a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl) optionally substituted by a C_{1-6} alkoxy-carbonyl group;

(3) a C_{3-10} cycloalkyl-carbonyl group (e.g., cyclopentylcarbonyl, cyclohexylcarbonyl);

(4) a C_{6-14} aryl-carbonyl group (e.g., benzoyl) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom, a cyano group, an optionally halogenated C_{1-6} alkyl group, a C_{1-6} alkoxy group, a carboxyl group, a C_{1-6} alkoxy-carbonyl group, an aromatic heterocyclic group (e.g., tetrazolyl, oxadiazolyl), a non-aromatic heterocyclic group (e.g., oxooxadiazolyl) and a carbamoyl group;

(5) a C_{7-13} aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl) optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(6) a carbamoyl group;

(7) a mono- or di-C_{1-6} alkyl-carbamoyl group (e.g., dimethylcarbamoyl);

(8) a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl);

(9) a C_{6-14} arylsulfonyl group optionally substituted by a C_{1-6} alkylsulfonyl group (e.g., phenylsulfonyl, methylsulfonylphenylsulfonyl);

(10) an aromatic heterocyclic (e.g., pyridyl, thiazolyl, oxazolyl, indolyl)-sulfonyl group optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group and a mono- or di-(C_{1-6} alkyl-carbonyl)-amino group (e.g., 2-acetylamino-4-methyl-5-thiazolylsulfonyl);

(11) a C_{7-13} aralkyl-carbonyl group (e.g., benzylcarbonyl, phenethylcarbonyl);

(12) a C_{8-13} arylalkenyl-carbonyl group (e.g., styrylcarbonyl);
(13) an aromatic heterocyclic (e.g., furyl, thienyl, xazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, pyrazinyl, benzofuryl, benzothienyl, quinoxalinyl)-carbonyl group (e.g., furylcarbonyl, thienylcarbonyl, thiazolylcarbonyl, pyrazolylcarbonyl, pyridylcarbonyl, pyrazinylcarbonyl, benzofurylcarbonyl, benzothienylcarbonyl, quinoxalinylcarbonyl) optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group, a C_{6-14} aryl group, a C_{7-13} aralkyl group, a C_{1-6} alkoxy group, a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;
(14) a nitrogen-containing heterocyclic (e.g., pyrrolidinyl, piperidinyl, piperazinyl, morpholino, oxopiperazinyl)-carbonyl group optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted by 1 to 3 substituent(s) selected from carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group), a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;
(15) a C_{6-14} aryl-nitrogen-containing heterocyclic (e.g., pyrrolidinyl, piperidinyl, piperazinyl, morpholino)-carbonyl group;
(16) a 4-oxo-4,5,6,7-tetrahydro-1-benzofuranyl-carbonyl group;
(17) a tetrahydropyranylcarbonyl group;
(18) a C_{6-14} aryloxy-carbonyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;
(19) a C_{7-13} aralkyl-carbamoyl group (e.g., benzylcarbamoyl);
(20) an aromatic heterocyclic (e.g., pyridyl, thiazolyl, oxazolyl, indolyl)-carbamoyl group (e.g., thiazolylcarbamoyl, oxazolylcarbamoyl) optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;
and the like, are preferable.

As preferable examples of the substituted amino group,

(1) a mono- or di-C_{1-10} alkylamino group (e.g., methylamino, dimethylamino, ethylamino, diethylamino, propylamino, dibutylamino);

(2) a mono- or di-C_{2-10} alkenylamino group (e.g., diallylamino);

(3) a mono- or di-C_{3-10} cycloalkylamino group (e.g., cyclohexylamino);

(4) a C_{6-14} arylamino group (e.g., phenylamino);

(5) a mono- or di-(C_{1-6} alkyl-carbonyl)-amino group (e.g., acetylamino, propionylamino, butanoylamino, isobutanoylamino, isopentanoylamino);

(6) a C_{1-6} alkoxy-carbonylamino group (e.g., methoxycarbonylamino) optionally substituted by C_{1-6} alkoxy-carbonyl group;

(7) a carbamoyl-C_{1-10} alkylamino group (e.g., carbamoylmethylamino);

(8) a C_{1-6} alkoxy-carbonyl-C_{1-10} alkylamino group (e.g., methoxycarbonylmethylamino, ethoxycarbonylmethylamino, tert-butoxycarbonylmethylamino);

(9) a carboxy-C_{1-10} alkylamino group (e.g., carboxymethylamino);

(10) a C_{3-10} cycloalkyl-carbonylamino group (e.g., cyclopentylcarbonylamino, cyclohexylcarbonylamino);

(11) a C_{6-14} aryl-carbonylamino group (e.g., benzoylamino) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom, a cyano group, an optionally halogenated C_{1-6} alkyl group, a C_{1-6} alkoxy group, a carboxyl group, a C_{1-6} alkoxy-carbonyl group, an aromatic heterocyclic group (e.g., tetrazolyl, oxadiazolyl), a non-aromatic heterocyclic group (e.g., oxooxadiazolyl) and a carbamoyl group;

(12) a C_{7-13} aralkyloxy-carbonylamino group (e.g., benzyloxycarbonylamino) optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-

carbonyl group and a carbamoyl group;

(13) a carbamoylamino group;

(14) a mono- or di-C_{1-6} alkyl-carbamoylamino group (e.g., dimethylcarbamoylamino);

(15) a C_{1-6} alkylsulfonylamino group (e.g., methylsulfonylamino);

(16) a C_{6-14} arylsulfonylamino group optionally substituted by a C_{1-6} alkylsulfonyl group (e.g., phenylsulfonylamino, methylsulfonylphenylsulfonylamino);

(17) an aromatic heterocyclic (e.g., pyridyl, thiazolyl, oxazolyl, indolyl)-sulfonylamino group optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group and a mono- or di-(C_{1-6} alkyl-carbonyl)-amino group (e.g., 2-acetylamino-4-methyl-5-thiazolylsulfonylamino);

(18) a C_{7-13} aralkyl-carbonylamino group (e.g., benzylcarbonylamino, phenethylcarbonylamino);

(19) a C_{8-13} arylalkenyl-carbonylamino group (e.g., styrylcarbonylamino);

(20) an aromatic heterocyclic (e.g., furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, pyrazinyl, benzofuryl, benzothienyl, quinoxalinyl)-carbonylamino group optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group, a C_{6-14} aryl group, a C_{7-13} aralkyl group, a C_{1-6} alkoxy group, a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(21) a nitrogen-containing heterocyclic (e.g., pyrrolidinyl, piperidinyl, piperazinyl, morpholino, oxopiperazinyl)-carbonylamino group optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group), a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(22) a C_{6-14} aryl-nitrogen-containing heterocyclic (e.g.,

pyrrolidinyl, piperidinyl, piperazinyl, morpholino)-carbonylamino group;

(23) a tetrahydropyranylcarbonylamino group;

(24) a 4-oxo-4,5,6,7-tetrahydro-1-benzofuranyl-carbonylamino group;

(25) a C_{6-14} aryloxy-carbonylamino group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(26) a C_{7-13} aralkyl-carbamoylamino group (e.g., benzylcarbamoylamino);

(27) an aromatic heterocyclic (e.g., pyridyl, thiazolyl, oxazolyl, indolyl)-carbamoylamino group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

and the like can be mentioned.

The "optionally substituted amino group" for R^4 is preferably an amino group optionally mono- or di-substituted by a C_{1-6} alkyl group (e.g., methyl, ethyl, propyl, isopropyl). R^4 is particularly preferably an amino group.

As the "divalent chain hydrocarbon group" for L or Q, for example, a divalent chain hydrocarbon group having 1 to 10 carbon atoms can be mentioned. Specific examples include

(1) a C_{1-10} alkylene group (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CHCH_3-$, $-C(CH_3)_2-$, $-(CH(CH_3))_2-$, $-(CH_2)_2C(CH_3)_2-$, $-(CH_2)_3C(CH_3)_2-$);

(2) a C_{2-10} alkenylene group (e.g., $-CH=CH-$, $-CH_2-CH=CH-$, $-CH=CH-CH_2-$, $-CH=CH-CH_2-CH_2-$, $-C(CH_3)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-CH=CH-CH=CH-$, $-CH=CH-CH_2-CH_2-CH_2-$);

(3) a C_{2-10} alkynylene group (e.g., $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH_2-C\equiv C-CH_2-CH_2-$)

and the like.

The "divalent chain hydrocarbon group" is preferably a C_{1-10} alkylene group or a C_{2-10} alkenylene group, more preferably $-CH_2-$, $-(CH_2)_2-$, $-CH=CH-$ and the like.

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L is preferably a C_{1-10} alkylene group, more preferably -CH_2- and the like.

Q is preferably a bond, a C_{1-10} alkylene group or a C_{2-10} alkenylene group, more preferably a bond, -CH_2-, -$(CH_2)_2$-, -CH=CH- and the like. Q is particularly preferably a bond.

As the "acyl group" for X, for example, a group represented by the formula: $-COR^5$, $-CO-OR^5$, $-SO_2R^5$, $-SOR^5$, $-PO_3R^5R^6$, $-CO-NR^{5a}R^{6a}$, $-CS-NR^{5a}R^{6a}$ [wherein R^5 and R^6 are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; R^{5a} and R^{6a} are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R^{5a} and R^{6a} may form an optionally substituted nitrogen-containing heterocycle together with the adjacent nitrogen atom], and the like can be mentioned.

As the "optionally substituted hydrocarbon group" for R^5, R^6, R^{5a} or R^{6a}, those exemplarily recited for the aforementioned R^1 or R^2 can be used.

As the "heterocyclic group" of the "optionally substituted heterocyclic group" for R^5, R^6, R^{5a} or R^{6a}, an aromatic heterocyclic group and a non-aromatic heterocyclic group can be mentioned.

As the aromatic heterocyclic group, those exemplarily recited for the "aromatic group" of the "optionally substituted aromatic group" for the aforementioned R^3 can be mentioned.

As the non-aromatic heterocyclic group, for example, a 5- to 7-membered monocyclic non-aromatic heterocyclic group containing 1 to 4 heteroatom(s) selected from an oxygen atom, a sulfur atom and a nitrogen atom as a ring-constituting atom, besides carbon atoms, and a fused non-aromatic heterocyclic group can be mentioned. As the fused non-aromatic heterocyclic group, for example, a group wherein these 5- to 7- membered monocyclic non-aromatic heterocyclic groups and a 6-membered

ring containing 1 or 2 nitrogen atom(s), a benzene ring or a 5-membered ring containing one sulfur atom are fused, and the like can be mentioned.

As preferable examples of the non-aromatic heterocyclic group, pyrrolidinyl (e.g., 1-pyrrolidinyl), piperidinyl (e.g., piperidino), morpholinyl (e.g., morpholino), thiomorpholinyl (e.g., thiomorpholino), piperazinyl (e.g., 1-piperazinyl), hexamethyleniminyl (e.g., hexamethylenimin-1-yl), oxazolidinyl (e.g., oxazolidin-3-yl), thiazolidinyl (e.g., thiazolidin-3-yl), imidazolidinyl (e.g., imidazolidin-3-yl), oxoimidazolidinyl (e.g., 2-oxoimidazolidin-1-yl), dioxoimidazolidinyl (e.g., 2,4-dioxoimidazolidin-3-yl), dioxooxazolidinyl (e.g., 2,4-dioxooxazolidin-3-yl, 2,4-dioxooxazolidin-5-yl, 2,4-dioxooxazolidin-1-yl), dioxothiazolidinyl (e.g., 2,4-dioxothiazolidin-3-yl, 2,4-dioxothiazolidin-5-yl), dioxoisoindolyl (e.g., 1,3-dioxoisoindol-2-yl), oxooxadiazolyl (e.g., 5-oxooxadiazol-3-yl), oxothiadiazolyl (e.g., 5-oxothiadiazol-3-yl), xopiperazinyl (e.g., 3-oxopiperazin-1-yl), dioxopiperazinyl (e.g., 2,3-dioxopiperazin-1-yl, 2,5-dioxopiperazin-1-yl), xodioxolyl (e.g., 2-oxo-1,3-dioxol-4-yl), oxodioxolanyl (e.g., 2-oxo-1,3-dioxolan-4-yl), oxo-2-benzofuranyl (e.g., 3-oxo-2-benzofuran-1-yl), oxodihydrooxadiazolyl (e.g., 5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl), 4-oxo-2-thioxo-1,3-thiazolidin-5-yl, 4-oxo-2-thioxo-1,3-oxazolidin-5-yl, tetrahydropyranyl (e.g., 4-tetrahydropyranyl), 4-oxo-4,5,6,7-tetrahydro-1-benzofuranyl (e.g., 4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-yl), 1,3(2H,5H)-dioxo-tetrahydroimidazo[1,5-a]pyridinyl, 1,3(2H,5H)-dioxo-10,10a-dihydroimidazo[1,5-b]isoquinolinyl and the like can be mentioned.

The "heterocyclic group" of the "optionally substituted heterocyclic group" for R^5, R^6, R^{5a} or R^{6a} optionally has 1 to 3 substituent(s) at substitutable position(s).

As these substituents, for example, those exemplarily

recited for the substituents for the C_{3-10} cycloalkyl group exemplarily recited for the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for the aforementioned R^1 or R^2 can be mentioned.

The substituents are preferably

a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);

a halogen atom (e.g., fluorine, chlorine, bromine, iodine);

a C_{6-14} aryl group;

a C_{7-13} aralkyl group;

a hydroxy group;

a C_{1-6} alkoxy group;

a carboxyl group;

a C_{1-6} alkoxy-carbonyl group;

a carbamoyl group;

a C_{1-6} alkyl group substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

a mono- or di-(C_{1-6} alkyl-carbonyl)-amino group;

and the like.

As the "nitrogen-containing heterocycle" of the "optionally substituted nitrogen-containing heterocycle" f rmed by R^{5a} and R^{6a} together with the adjacent nitrogen atom, for example, a 5- to 7-membered nitrogen-containing heterocycle containing at least one nitrogen atom and optionally further containing 1 to 2 heteroatom(s) selected from an oxygen atom, a sulfur atom and a nitrogen atom as a ring-constituting atom, besides carbon atoms can be mentioned. As preferable examples of the "nitrogen-containing heterocycle", pyrrolidine, imidazolidine, pyrazolidine, piperidine, piperazine, morpholine, thiomorpholine, oxopiperazine and the like can be mentioned.

The nitrogen-containing heterocycle optionally has 1 to

3 (preferably 1 or 2) substituent(s) at substitutable position(s). As these substituents,

a hydroxy group;

a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);

a C_{7-13} aralkyl group (e.g., benzyl, diphenylmethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);

a C_{6-14} aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);

a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl);

a C_{1-6} alkyl group substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

a carboxyl group;

a carbamoyl group;

and the like can be mentioned.

As preferable examples of the "acyl group",

(1) a formyl group;

(2) a carboxyl group;

(3) a carbamoyl group;

(4) a C_{1-6} alkyl-carbonyl group (e.g., acetyl, isobutanoyl, isopentanoyl);

(5) a C_{1-6} alkoxy-carbonyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a carbamoyl group, a thiocarbamoyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkyl-carbonyloxy group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl; carboxymethoxycarbonyl, carboxyethoxycarbonyl, carboxybutoxycarbonyl; carbamoylmethoxycarbonyl; thiocarbamoylmethoxycarbonyl; ethoxycarbonylmethoxycarbonyl, ethoxycarbonylethoxycarbonyl, methoxycarbonylbutoxycarbonyl,

ethoxycarbonylbutoxycarbonyl; tert-butylcarbonyloxymethoxycarbonyl);

(6) an aromatic heterocyclic (e.g., furyl, thienyl, pyridyl, thiazolyl, oxazolyl, pyrazinyl, indolyl)-C_{1-6} alkoxy-carbonyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a carbamoyl group, a thiocarbamoyl group and a C_{1-6}alkoxy-carbonyl group (e.g., pyridylmethoxycarbonyl; carboxythiazolylmethoxycarbonyl; carbamoylthiazolylmethoxycarbonyl; ethoxycarbonylthiazolylmethoxycarbonyl);

(7) a non-aromatic heterocyclic (e.g., oxodioxolyl, oxodioxolanyl, oxo-2-benzofuranyl)-C_{1-6} alkoxy-carbonyl group optionally substituted by a C_{1-6} alkyl group (e.g., methyloxodioxolylmethoxycarbonyl, oxo-2-benzofuranylethoxycarbonyl);

(8) a C_{3-10} cycloalkyl-carbonyl group (e.g., cyclopentylcarbonyl, cyclohexylcarbonyl);

(9) a C_{6-14} aryl-carbonyl group (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom, a cyano group, an optionally halogenated C_{1-6}alkyl group (i.e., C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine)), a C_{1-6} alkoxy group, a carboxyl group, a C_{1-6} alkoxy-carbonyl group, an aromatic heterocyclic group (e.g., tetrazolyl, oxadiazolyl), a non-aromatic heterocyclic group (e.g., oxooxadiazolyl) and a carbamoyl group;

(10) a C_{6-14} aryloxy-carbonyl group (e.g., phenyloxycarbonyl, naphthyloxycarbonyl) optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(11) a C_{7-13} aralkyloxy-carbonyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a carbamoyl group, a thiocarbamoyl group, a C_{1-6} alkoxy-carbonyl

group, a halogen atom, a cyano group, a nitro group, a C_{1-6} alkoxy group, a C_{1-6} alkylsulfonyl group and a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted by 1 to 3 substituent(s) selected from a halogen atom, a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group) (e.g., benzyloxycarbonyl, phenethyloxycarbonyl; carboxybenzyloxycarbonyl; methoxycarbonylbenzyloxycarbonyl, biphenylylmethoxycarbonyl);

(12) a carbamoyl group mono- or di-substituted by a C_{1-6} alkyl group optionally substituted by 1 to 3 substituent(s) selected from halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and a C_{1-6} alkoxy group (e.g., methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, isobutylcarbamoyl, trifluoroethylcarbamoyl, N-methoxyethyl-N-methylcarbamoyl);

(13) a carbamoyl-C_{1-6} alkyl-carbamoyl group optionally mono- or di-substituted by a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine) (e.g., carbamoylmethylcarbamoyl, carbamoylethylcarbamoyl, dimethylcarbamoylmethylcarbamoyl, dimethylcarbamoylethylcarbamoyl);

(14) a C_{1-6} alkoxy-carbonyl-C_{1-6} alkyl-carbamoyl group optionally substituted by a C_{1-6} alkyl group (e.g., methoxycarbonylmethylcarbamoyl, ethoxycarbonylethylcarbamoyl, N-ethoxycarbonylmethyl-N-methylcarbamoyl);

(15) a C_{6-14} aryl-carbamoyl group (e.g., phenylcarbamoyl) optionally substituted by 1 to 3 substituent(s) selected from an amino group optionally mono- or di-substituted by a C_{1-6} alkyl group, a carboxyl group, a C_{1-6} alkoxy-carbonyl group, an aromatic heterocyclic group (e.g., tetrazolyl, oxadiazolyl), a non-aromatic heterocyclic group (e.g., oxooxadiazolyl) and a carbamoyl group;

(16) a mono- or di-C_{3-10} cycloalkyl-carbamoyl group optionally

substituted by a C_{1-6} alkyl group (e.g., cyclopropylcarbamoyl, cyclopentylcarbamoyl, dicyclohexylcarbamoyl, N-cyclohexyl-N-methylcarbamoyl);

(17) a C_{7-13} aralkyl-carbamoyl group optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a hydroxy group, a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkyl group (e.g., benzylcarbamoyl, phenethylcarbamoyl, phenylpropylcarbamoyl, hydroxyphenethylcarbamoyl, chlorobenzylcarbamoyl, methoxycarbonylbenzylcarbamoyl, N-benzyl-N-methylcarbamoyl);

(18) an aromatic heterocyclic (e.g., pyridyl, thienyl, furyl, thiazolyl, oxazolyl, indolyl)-C_{1-6} alkyl-carbamoyl group (e.g., indolylethylcarbamoyl, pyridylmethylcarbamoyl, thienylmethylcarbamoyl, thiazolylmethylcarbamoyl) optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a carbamoyl group and a C_{1-6} alkoxy-carbonyl group;

(19) a C_{1-6} alkylsulfonyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a carbamoyl group and a C_{1-6} alkoxy-carbonyl group (e.g., methylsulfonyl, carboxymethylsulfonyl);

(20) a C_{6-14} arylsulfonyl group optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group, a carboxyl group, a carbamoyl group, a thiocarbamoyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkylsulfonyl group (e.g., phenylsulfonyl; methylphenylsulfonyl; carboxyphenylsulfonyl; methoxycarbonylphenylsulfonyl; methylsulfonylphenylsulfonyl);

(21) a nitrogen-containing heterocyclic (e.g., pyrrolidinyl, piperidinyl, piperazinyl, morpholino, oxopiperazinyl)-carbonyl group optionally substituted by 1 to 3 substituent(s) selected from a hydroxy group, a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group), a carboxyl group, a C_{1-6} alkoxy-carbonyl

group and a carbamoyl group (e.g., pyrrolidinylcarbonyl, piperidinylcarbonyl, piperazinylcarbonyl, oxopiperazinylcarbonyl, morpholinocarbonyl, methoxycarbonylpyrrolidinylcarbonyl);

(22) a C_{6-14} aryl-nitrogen-containing heterocyclic (e.g., pyrrolidinyl, piperidinyl, piperazinyl, morpholino)-carbonyl group (e.g., phenylpiperazinylcarbonyl, phenylpiperidinylcarbonyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);

(23) a C_{7-13} aralkyl-nitrogen-containing heterocyclic (e.g., pyrrolidinyl, piperidinyl, piperazinyl, morpholino)-carbonyl group (e.g., benzylpiperazinylcarbonyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);

(24) an aromatic heterocyclic (e.g., pyridyl, thiazolyl, oxazolyl, indolyl)-sulfonyl group optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group and a mono- or di-(C_{1-6} alkyl-carbonyl)-amino group (e.g., 2-acetylamino-4-methyl-5-thiazolylsulfonyl);

(25) a non-aromatic heterocyclic (e.g., oxodioxolyl, oxodioxolanyl, oxo-2-benzofuranyl)oxy-carbonyl group (e.g., oxodioxolanyloxycarbonyl, oxo-2-benzofuranyloxycarbonyl);

(26) a C_{1-6} alkylsulfinyl group (e.g., methylsulfinyl);

(27) a thiocarbamoyl group;

(28) a phosphono group optionally mono- or di- substituted by a C_{1-6} alkyl group (e.g., dimethyl phosphono, diethyl phosphono);

(29) a C_{7-13} aralkyl-carbonyl group (e.g., benzylcarbonyl, phenethylcarbonyl);

(30) a C_{8-13} arylalkenyl-carbonyl group (e.g., styrylcarbonyl);

(31) an aromatic heterocyclic (e.g., furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, pyrazinyl, benzofuryl, benzothienyl, quinoxalinyl)-carbonyl group (e.g., furylcarbonyl, thienylcarbonyl, thiazolylcarbonyl, pyrazolylcarbonyl, pyridylcarbonyl, pyrazinylcarbonyl,

benzofurylcarbonyl, benzothienylcarbonyl, quinoxalinylcarbonyl) optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group, a C_{6-14} aryl group, a C_{7-13} aralkyl group, a C_{1-6} alkoxy group, a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(32) a tetrahydropyranylcarbonyl group;

(33) a 4-oxo-4,5,6,7-tetrahydro-1-benzofuranyl-carbonyl group;

(34) a C_{3-10} cycloalkyl-C_{1-6} alkoxy-carbonyl group (e.g., cyclohexylmethoxycarbonyl) optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(35) an aromatic heterocyclic (e.g., thienyl, furyl, pyridyl, oxazolyl, thiazolyl, tetrazolyl, pyridyl, quinolyl, indolyl)-C_{7-13} aralkyloxy-carbonyl group (e.g., tetrazolylbenzyloxycarbonyl);

(36) an aromatic heterocyclic (e.g., thienyl, furyl, pyridyl, thiazolyl, oxazolyl, indolyl)-carbamoyl group (e.g., thienylcarbamoyl, furylcarbamoyl, thiazolylcarbamoyl, oxazolylcarbamoyl) optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

and the like can be mentioned.

The "acyl group" for X is preferably

(1) a carboxyl group;

(2) a carbamoyl group;

(3) a C_{1-6} alkoxy-carbonyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a carbamoyl group, a thiocarbamoyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkyl-carbonyloxy group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl; carboxymethoxycarbonyl, carboxyethoxycarbonyl, carboxybutoxycarbonyl; carbamoylmethoxycarbonyl; thiocarbamoylmethoxycarbonyl; ethoxycarbonylmethoxycarbonyl, ethoxycarbonylethoxycarbonyl, methoxycarbonylbutoxycarbonyl,

ethoxycarbonylbutoxycarbonyl; tert-butylcarbonyloxymethoxycarbonyl);

(4) a carbamoyl group mono- or di-substituted by a C_{1-6} alkyl group optionally substituted by 1 to 3 substituent(s) selected from a halogen atom and a C_{1-6} alkoxy group (e.g., methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, isobutylcarbamoyl, trifluoroethylcarbamoyl, N-methoxyethyl-N-methylcarbamoyl);

(5) a carbamoyl-C_{1-6} alkyl-carbamoyl group optionally mono- or di-substituted by a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atom(s) (e.g., carbamoylmethylcarbamoyl, carbamoylethylcarbamoyl, dimethylcarbamoylmethylcarbamoyl, dimethylcarbamoylethylcarbamoyl);

and the like. Of these, a carboxyl group is preferable.

As the "substituted hydroxy group" for X, for example, a hydroxy group substituted by a substituent selected from a C_{1-10} alkyl group, a C_{2-10} alkenyl group, a C_{3-10} cycloalkyl group, a C_{3-10} cycloalkenyl group, a C_{6-14} aryl group, a C_{7-13} aralkyl group, a C_{8-13} arylalkenyl group, a C_{1-6} alkyl-carbonyl group (e.g., acetyl, isobutanoyl, isopentanoyl), a 5- or 6-membered aromatic heterocyclic group (e.g., furyl, thienyl, thiazolyl, oxazolyl, imidazolyl, triazolyl, pyrazolyl, pyrimidinyl), a fused aromatic heterocyclic group (e.g., indolyl) and the like, each of which is optionally substituted, can be mentioned.

As the C_{1-10} alkyl group, a C_{2-10} alkenyl group, a C_{3-10} cycloalkyl group, a C_{3-10} cycloalkenyl group, a C_{6-14} aryl group, a C_{7-13} aralkyl group and a C_{8-13} arylalkenyl group here, those exemplarily recited for the "hydrocarbon group" f the "optionally substituted hydrocarbon group" for the aforementioned R^1 or R^2 can be used.

The aforementioned C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group, C_{6-14}

aryl group, C_{7-13} aralkyl group, C_{8-13} arylalkenyl group, C_{1-6} alkyl-carbonyl group, 5- or 6-membered aromatic heterocyclic group and fused aromatic heterocyclic group each optionally have 1 to 3 substituent(s) at substitutable position(s). As these substituents, for example,

a halogen atom (e.g., fluorine, chlorine, bromine, iodine);

a hydroxy group;

a cyano group;

a C_{1-6} alkyl group optionally substituted by 1 or 2 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a carboxyl group, a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, tert-butoxycarbonyl) and a carbamoyl group;

a C_{1-6} alkoxy group optionally substituted by 1 or 2 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a carboxyl group and a C_{1-6} alkoxy-carbonyl group (e.g., tert-butoxycarbonyl);

a C_{1-6} alkylthio group (e.g., methylthio, ethylthio);

a C_{1-6} alkyl-carbonyl group;

a carboxyl group;

a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl);

a carbamoyl group optionally mono- or di-substituted by a C_{1-10} alkyl group (e.g., methyl, ethyl, propyl, isopropyl, neopentyl);

an amino group optionally mono- or di-substituted by a C_{1-10} alkyl group (e.g., methyl, ethyl, propyl, isopropyl, neopentyl);

a C_{1-6} alkyl-carbonylamino group;

an aromatic heterocyclic group (e.g., furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridyl) optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group (e.g., methyl, ethyl), carboxyl group, a C_{1-6} alkoxy-carbonyl group (e.g.,

methoxycarbonyl, ethoxycarbonyl) and a carbamoyl group;
a C_{1-6} alkylsulfinyl group (e.g., methylsulfinyl);
a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl);
and the like can be mentioned.

As preferable examples of the "substituted hydroxy group",
(1) a C_{1-6} alkyl-carbonyloxy group;
(2) a C_{1-10} alkoxy group optionally substituted by 1 to 3 substituent(s) selected from a hydroxy group, a carboxyl group, a carbamoyl group and a C_{1-6} alkoxy-carbonyl group;
(3) a C_{6-14} aryloxy group optionally substituted by 1 to 3 substituent(s) selected from a halogen atom, a carboxyl group, a C_{1-6} alkoxy-carbonyl group, a C_{1-6} alkylthio group, a carbamoyl group, a C_{1-6} alkoxy group, a C_{1-6} alkylsulfonyl group, a C_{1-6} alkylsulfinyl group and a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted by 1 or 2 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group);
(4) a 5- or 6-membered aromatic heterocyclyloxy group (preferably thienyloxy, thiazolyloxy, oxazolyloxy, imidazolyloxy, triazolyloxy, pyrazolyloxy, pyridyloxy, pyrimidinyloxy) optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted by 1 to 2 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group), a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;
(5) a fused aromatic heterocyclyloxy group (preferably indolyloxy) optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;
(6) an aromatic heterocyclic (preferably pyridyl)-C_{1-6} alkoxy group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a

carbamoyl group;

(7) an aromatic heterocyclic (preferably tetrazolyl)-C_{6-14} aryloxy group;

and the like can be mentioned.

As the "optionally substituted thiol group" for X, for example, a thiol group optionally substituted by a substituent selected from a C_{1-10} alkyl group, a C_{2-10} alkenyl group, a C_{3-10} cycloalkyl group, a C_{3-10} cycloalkenyl group, a C_{6-14} aryl group, a C_{7-13} aralkyl group, a C_{8-13} arylalkenyl group, a C_{1-6} alkyl-carbonyl group (e.g., acetyl, isobutanoyl, isopentanoyl), a 5- or 6-membered aromatic heterocyclic group (e.g., furyl, thienyl, thiazolyl, oxazolyl, imidazolyl, triazolyl, pyrazolyl, pyrimidinyl), a fused aromatic heterocyclic group (e.g., indolyl) and the like, each of which is optionally substituted, can be mentioned.

As the C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group, C_{6-14} aryl group, C_{7-13} aralkyl group and C_{8-13} arylalkenyl group here, those exemplarily recited for the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for the aforementioned R^1 or R^2 can be used.

The aforementioned C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group, C_{6-14} aryl group, C_{7-13} aralkyl group, C_{8-13} arylalkenyl group, C_{1-6} alkyl-carbonyl group, 5- or 6-membered aromatic heterocyclic group and fused aromatic heterocyclic group each optionally have 1 to 3 substituent(s) at substitutable position(s). As these substituents, the substituents for the C_{1-10} alkyl group and the like for the "substituted hydroxy group" for the aforementioned X can be used.

As preferable examples of the "optionally substituted thiol group",

(1) a C_{1-6} alkylthio group optionally substituted by 1 to 3 substituent(s) selected from a hydroxy group, a carboxyl group,

a carbamoyl group and a C_{1-6} alkoxy-carbonyl group;

(2) a C_{6-14} arylthio group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group, a C_{1-6} alkylthio group and a carbamoyl group;

(3) a 5 or 6-membered aromatic heterocyclylthio group (preferably thienylthio, thiazolylthio, oxazolylthio, imidazolylthio, triazolylthio, pyrazolylthio, pyridylthio, pyrimidinylthio) optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group, a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

and the like can be mentioned.

As the "optionally substituted amino group" for X, those exemplarily recited for the aforementioned R^4 can be used.

As the "cyclic group" of the "optionally substituted cyclic group" for X, for example, an aromatic hydrocarbon group, a non-aromatic cyclic hydrocarbon group, an aromatic heterocyclic group, a non-aromatic heterocyclic group and the like can be mentioned.

As the aromatic hydrocarbon group and the aromatic heterocyclic group, those exemplarily recited for the "aromatic group" of the "optionally substituted aromatic group" for the aforementioned R^3 can be used.

In addition, as the non-aromatic heterocyclic group, those exemplarily recited for the "heterocyclic group" of the "optionally substituted heterocyclic group" for the aforementioned R^5 can be used.

As the non-aromatic cyclic hydrocarbon group, for example, a C_{3-10} cycloalkyl group, a C_{3-10} cycloalkenyl group, a C_{4-10} cycloalkadienyl group and the like, each of which is optionally fused with a benzene ring, can be mentioned.

As the C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group and C_{4-10} cycloalkadienyl group here, those exemplarily recited for the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for the af rementioned R^1 or R^2 can be used.

The "cyclic group" of the "optionally substituted cyclic group" for X optionally has 1 t 3 substituent(s) at substitutable position(s).

As these substituents, for example, those exemplarily recited for the substituents for the C_{3-16} cycloalkyl group exemplarily recited for the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for the aforementioned R^1 or R^2 can be mentioned.

The substituents are preferably

a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a carbamoyl group, a carboxyl group and a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl);

a halogen atom (e.g., fluorine, chlorine, bromine, iodine);

a carboxyl group;

a C_{1-6} alkoxy-carbonyl group;

a carbamoyl group;

and the like.

X is preferably an acyl group, a substituted hydroxy group, an optionally substituted thiol group or an optionally substituted amino group, more preferably an acyl group. Of these,

(1) a carboxyl group;

(2) a carbamoyl group;

(3) a C_{1-6} alkoxy-carbonyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a carbamoyl group, a thiocarbamoyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkyl-carbonyloxy group;

(4) a carbamoyl group mono- or di-substituted by a C_{1-6} alkyl group optionally substituted by 1 to 3 substituent(s) selected from a halogen atom and a C_{1-6} alkoxy group;

(5) a carbamoyl-C_{1-6} alkyl-carbamoyl group optionally mono- or di-substituted by a C_{1-6} alkyl group optionally substituted by

1 to 3 halogen atom(s);

and the like are preferable, and a carboxyl group is particularly preferable.

Of compound (I), when X is an ethoxycarbonyl group, then Q is a divalent chain hydrocarbon group.

Moreover, compound (I) does not comprise

2,6-diisopropyl-3-methylaminomethyl-4-(4-fluorophenyl)-5-pentylpyridine [this compound is also designated as {[4-(4-fluorophenyl)-2,6-diisopropyl-5-pentylpyridin-3-yl]methyl}methylamine];

2,6-diisopropyl-3-aminomethyl-4-(4-fluorophenyl)-5-pentylpyridine [this compound is also designated as {[4-(4-fluorophenyl)-2,6-diisopropyl-5-pentylpyridin-3-yl]methyl}amine];

2,6-diisopropyl-3-(dimethylamino)methyl-4-(4-fluorophenyl)-5-pentylpyridine [this compound is also designated as 1-[4-(4-fluorophenyl)-2,6-diisopropyl-5-pentylpyridin-3-yl]-N,N-dimethylmethaneamine];

2,6-diisopropyl-3-(ethylamino)methyl-4-(4-fluorophenyl)-5-pentylpyridine [this compound is also designated as N-{[4-(4-fluorophenyl)-2,6-diisopropyl-5-pentylpyridin-3-yl]methyl}ethaneamine]; and

3-(tert-butyldimethylsilyloxymethyl)-2,6-diisopropyl-4-(4-fluorophenyl)-5-(indolyl-5-aminomethyl)pyridine [this compound is also designated as N-{[5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-4-(4-fluorophenyl)-2,6-diisopropylpyridin-3-yl]methyl}-1H-indol-5-amine].

As preferable examples of compound (I), the following compounds can be mentioned.

[Compound A]

A compound wherein

R^1 and R^2 are the same or different and each is a C_{1-10} alkyl group (preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, neopentyl) optionally substituted by 1 to 3

substituent(s) selected from a C_{3-10} cycloalkyl group (preferably cyclopropyl), a C_{1-6} alkoxy-carbonyl group (preferably methoxycarbonyl) and the like;

R^3 is a C_{6-14} aryl group (the C_{6-14} aryl group is preferably phenyl) optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a halogen atom (e.g., fluorine, chlorine, bromine, iodine) and the like;

R^4 is an amino group optionally mono- or di-substituted by a C_{1-6} alkyl group (e.g., methyl, ethyl, propyl, isopropyl);

L is a C_{1-10} alkylene group (preferably $-CH_2-$);

Q is a bond, a C_{1-10} alkylene group or a C_{2-10} alkenylene group (preferably a bond, $-CH_2-$, $-(CH_2)_2-$, $-CH=CH-$); and

X is a carboxyl group;

a carbamoyl group;

a C_{1-6} alkoxy-carbonyl group;

a carbamoyl group mono- or di-substituted by a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atom(s);

or

a carbamoyl-C_{1-6} alkyl-carbamoyl group optionally mono- or di-substituted by a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atom(s).

[Compound B]

A compound wherein

R^1 and R^2 are the same or different and each is

(1) a C_{1-10} alkyl group optionally substituted by 1 to 3 substituent(s) selected from a C_{3-10} cycloalkyl group (preferably cyclopropyl), a C_{1-6} alkoxy-carbonyl group, a C_{1-6} alkoxy group and the like;

(2) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom, a carboxyl group, a C_{1-6} alkoxy-carbonyl group, a carbamoyl group and the like; or

(3) a C_{7-13} aralkyl group (preferably benzyl);

R^3 is a C_{6-14} aryl group (the C_{6-14} aryl group is preferably phenyl) optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atom(s), a halogen atom, a C_{1-6} alkoxy-carbonyl group, a carboxyl group, a hydroxy group, a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atom(s), and the like;

R^4 is an amino group optionally mono- or di- substituted by a C_{1-6} alkyl group (preferably an amino group);

L is a C_{1-10} alkylene group (preferably $-CH_2-$);

Q is a bond, a C_{1-10} alkylene group or a C_{2-10} alkenylene group (preferably a bond, $-CH_2-$, $-(CH_2)_2-$, $-CH=CH-$); and

X is

(1) a hydrogen atom;

(2) a cyano group;

(3) (3a) a carboxyl group;

(3b) a carbamoyl group;

(3c) a C_{1-6} alkoxy-carbonyl group optionally substituted by substituent(s) selected from a carboxyl group, a carbamoyl group, a thiocarbamoyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkyl-carbonyloxy group;

(3d) an aromatic heterocyclic (preferably pyridyl, thiazolyl, oxazolyl, indolyl)-C_{1-6} alkoxy-carbonyl group optionally substituted by substituent(s) selected from a carboxyl group, a carbamoyl group, a thiocarbamoyl group and a C_{1-6} alkoxy-carbonyl group;

(3e) a non-aromatic heterocyclic (preferably oxodioxolyl, oxodioxolanyl, oxo-2-benzofuranyl)-C_{1-6} alkoxy-carbonyl group optionally substituted by a C_{1-6} alkyl group;

(3f) a C_{7-13} aralkyloxy-carbonyl group optionally substituted by substituent(s) selected from a carboxyl group, carbamoyl group, a thiocarbamoyl group and a C_{1-6} alkoxy-carbonyl group;

(3g) a carbamoyl group mono- or di-substituted by a C_{1-6}

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alkyl group optionally substituted by substituent(s) selected from 1 to 3 halogen atom(s) and a C_{1-6} alkoxy group;

(3h) a carbamoyl-C_{1-6} alkyl-carbamoyl group optionally mono- or di-substituted by a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atom(s);

(3i) a C_{1-6} alkoxy-carbonyl-C_{1-6} alkyl-carbamoyl group optionally substituted by a C_{1-6} alkyl group;

(3j) a mono- or di-C_{3-10} cycloalkyl-carbamoyl group optionally substituted by a C_{1-6} alkyl group;

(3k) a C_{7-13} aralkyl-carbamoyl group optionally substituted by substituent(s) selected from a halogen atom, a hydroxy group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkyl group;

(3l) an aromatic heterocyclic (preferably pyridyl, thiazolyl, oxazolyl, indolyl)-C_{1-6} alkyl-carbamoyl group;

(3m) a C_{1-6} alkylsulfonyl group optionally substituted by substituent(s) selected from a carboxyl group, a carbamoyl group and a C_{1-6} alkoxy-carbonyl group;

(3n) a C_{6-14} arylsulfonyl group optionally substituted by substituent(s) selected from a C_{1-6} alkyl group, a carboxyl group, a carbamoyl group, a thiocarbamoyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkylsulfonyl group;

(3o) a nitrogen-containing heterocyclic (preferably pyrrolidinyl, piperidino, piperazinyl, morpholino)-carbonyl group optionally substituted by substituent(s) selected from a hydroxy group and a C_{1-6} alkoxy-carbonyl group;

(3p) a C_{6-14} aryl-nitrogen-containing heterocyclic (preferably pyrrolidinyl, piperidino, piperazinyl, morpholino)-carbonyl group optionally substituted by a halogen atom;

(3q) a C_{7-13} aralkyl-nitrogen-containing heterocyclic (preferably pyrrolidinyl, piperidino, piperazinyl, morpholino)-carbonyl group optionally substituted by a halogen atom;

(3r) a non-aromatic heterocyclic (preferably oxodioxolyl, oxodioxolanyl, oxo-2-benzofuranyl)oxy-carbonyl group; or

(3s) a phosphono group optionally mono- or di-substituted by a C_{1-6} alkyl group;

(4) a C_{1-6} alkyl-carbonyloxy group;

(5) (5a) a C_{1-6} alkylthio group optionally substituted by substituent(s) selected from a carboxyl group, a carbamoyl group and a C_{1-6} alkoxy-carbonyl group;

(5b) a C_{6-14} arylthio group (preferably phenylthio) optionally substituted by substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkylthio group; or

(5c) a 5-membered aromatic heterocyclylthio group (preferably thiazolylthio, oxazolylthio, triazolylthio) optionally substituted by a C_{1-6} alkyl group;

(6) (6a) an amino group;

(6b) a C_{1-6} alkoxy-carbonyl-C_{1-10} alkylamino group (preferably methoxycarbonylmethylamino, ethoxycarbonylmethylamino, tert-butoxycarbonylmethylamino);

(6c) a carboxy-C_{1-10} alkylamino group;

(6d) a C_{7-13} aralkyloxy-carbonylamino group;

(6e) a carbamoylamino group;

(6f) a mono- or di-C_{1-6} alkyl-carbamoylamino group;

(6g) a C_{1-6} alkylsulfonylamino group;

(6h) a C_{6-14} arylsulfonylamino group optionally substituted by a C_{1-6} alkylsulfonyl group; or

(6i) an aromatic heterocyclic (e.g., pyridyl, thiazolyl, oxazolyl, indolyl)-sulfonylamino group optionally substituted by substituent(s) selected from a C_{1-6} alkyl group and a mono- or di-(C_{1-6} alkyl-carbonyl)-amino group; or

(7) tetrazolyl, oxoimidazolidinyl (preferably 2-oxoimidazolidin-1-yl), dioxoimidazolidinyl (preferably 2,4-dioxoimidazolidin-3-yl), oxopiperazinyl (preferably 3-oxopiperazin-1-yl), dioxopiperazinyl (preferably 2,3-dioxopiperazin-1-yl, 2,5-dioxopiperazin-1-yl) or oxodihydrooxadiazolyl (preferably 5-oxo-4,5-dihydro-1,2,4-

oxadiazol-3-yl).

[Compound C]

A compound wherein R^4 is an amino group, and X is any of the aforementioned (3a)-(3s) in the aforementioned Compound B.

[Compound D]

A compound wherein

R^1, R^2, R^3, R^4, L and Q are as defined for the aforementioned Compound B, X is

(1) a hydrogen atom;

(2) a cyano group;

(3) (3a) a carboxyl group;

(3b) a carbamoyl group;

(3c) a C_{1-6} alkoxy-carbonyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a carbamoyl group, a thiocarbamoyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkyl-carbonyloxy group;

(3d) an aromatic heterocyclic (preferably furyl, thienyl, pyridyl, thiazolyl, oxazolyl, pyrazinyl, indolyl)-C_{1-6} alkoxy-carbonyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a carbamoyl group, a thiocarbamoyl group and a C_{1-6} alkoxy-carbonyl group;

(3e) a non-aromatic heterocyclic (preferably oxodioxolyl, oxodioxolanyl, oxo-2-benzofuranyl)-C_{1-6} alkoxy-carbonyl group optionally substituted by a C_{1-6} alkyl group;

(3f) a C_{7-13} aralkyloxy-carbonyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a carbamoyl group, a thiocarbamoyl group, a C_{1-6} alkoxy-carbonyl group, a halogen atom, a cyano group, a nitro group, a C_{1-6} alkoxy group, a C_{1-6} alkylsulfonyl group and a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted by 1 to 3 substituent(s) selected from a halogen atom, a carboxyl group, C_{1-6} alkoxy-carbonyl group and a carbamoyl group);

(3g) a carbamoyl group mono- or di-substituted by a C_{1-6} alkyl group optionally substituted by 1 to 3 substituent(s)

selected from a halogen atom and a C_{1-6} alkoxy group;

(3h) a carbamoyl-C_{1-6} alkyl-carbamoyl group optionally mono- or di-substituted by a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atom(s);

(3i) a C_{1-6} alkoxy-carbonyl-C_{1-6} alkyl-carbamoyl group optionally substituted by a C_{1-6} alkyl group;

(3j) a mono- or di-C_{3-10} cycloalkyl-carbamoyl group optionally substituted by a C_{1-6} alkyl group;

(3k) a C_{7-13} aralkyl-carbamoyl group optionally substituted by 1 to 3 substituent(s) selected from a halogen atom, a hydroxy group, a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkyl group;

(3l) an aromatic heterocyclic (preferably pyridyl, thienyl, furyl, thiazolyl, oxazolyl, indolyl)-C_{1-6} alkyl-carbamoyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a carbamoyl group and a C_{1-6} alkoxy-carbonyl group;

(3m) a C_{1-6} alkylsulfonyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a carbamoyl group and a C_{1-6} alkoxy-carbonyl group;

(3n) a C_{6-14} arylsulfonyl group optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group, a carboxyl group, a carbamoyl group, a thiocarbamoyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkylsulfonyl group;

(3o) a nitrogen-containing heterocyclic (preferably pyrrolidinyl, piperidinyl, piperazinyl, morpholino)-carbonyl group optionally substituted by 1 to 3 substituent(s) selected from a hydroxy group, a carboxyl group and a C_{1-6} alkoxy-carbonyl group;

(3p) a C_{6-14} aryl-nitrogen-containing heterocyclic (preferably pyrrolidinyl, piperidinyl, piperazinyl, morpholino)-carbonyl group optionally substituted by 1 to 3 halogen atom(s);

(3q) a C_{7-13} aralkyl-nitrogen-containing heterocyclic

(preferably pyrrolidinyl, piperidinyl, piperazinyl, morpholino)-carbonyl group optionally substituted by 1 to 3 halogen atom(s);

(3r) a non-aromatic heterocyclic (preferably oxodioxolyl, oxodioxolanyl, oxo-2-benzofuranyl)oxy-carbonyl group;

(3s) a phosphono group optionally mono- or di-substituted by a C_{1-6} alkyl group;

(3t) an aromatic heterocyclic (preferably tetrazoyly)-C_{7-13} aralkyloxy-carbonyl group;

(3u) a C_{3-10} cycloalkyl-C_{1-6} alkoxy-carbonyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(3v) a C_{6-14} aryl-carbamoyl group optionally substituted by 1 to 3 substituent(s) selected from an amino group optionally mono- or di-substituted by a C_{1-6} alkyl group, a carboxyl group, a C_{1-6} alkoxy-carbonyl group, an aromatic heterocyclic group (preferably tetrazolyl, oxadiazolyl), a non-aromatic heterocyclic group (preferably oxooxadiazolyl) and a carbamoyl group; or

(3w) an aromatic heterocyclic (preferably thienyl, furyl)-carbamoyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(4) (4a) a C_{1-6} alkyl-carbonyloxy group;

(4b) a C_{1-10} alkoxy group optionally substituted by 1 to 3 substituent(s) selected from a hydroxy group, a carboxyl group, a carbamoyl group and a C_{1-6} alkoxy-carbonyl group;

(4c) a C_{6-14} aryloxy group optionally substituted by 1 to 3 substituent(s) selected from a halogen atom, a carboxyl group, a C_{1-6} alkoxy-carbonyl group, a C_{1-6} alkylthio group, a carbamoyl group, a C_{1-6} alkoxy group, a C_{1-6} alkylsulfonyl group, a C_{1-6} alkylsulfinyl group and a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted by 1 or 2

substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group);

(4d) a 5- or 6-membered aromatic heterocyclyloxy group (preferably thienyloxy, thiazolyloxy, oxazolyloxy, imidazolyloxy, triazolyloxy, pyrazolyloxy, pyridyloxy, pyrimidinyloxy) optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted by 1 or 2 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group), a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(4e) a fused aromatic heterocyclyloxy group (preferably indolyloxy) optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(4f) an aromatic heterocyclic (preferably pyridyl)-C_{1-6} alkoxy group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group; or

(4g) an aromatic heterocyclic (preferably tetrazolyl)-C_{6-14} aryloxy group;

(5) (5a) a C_{1-6} alkylthio group optionally substituted by 1 to 3 substituent(s) selected from a hydroxy group, a carboxyl group, a carbamoyl group and a C_{1-6} alkoxy-carbonyl group;

(5b) a C_{6-14} arylthio group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group, a C_{1-6} alkylthio group and a carbamoyl group; or

(5c) a 5- or 6-membered aromatic heterocyclylthio group (preferably thienylthio, thiazolylthio, oxazolylthio, imidazolylthio, triazolylthio, pyrazolylthio, pyridylthio, pyrimidinylthio) optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group, a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

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(6) (6a) an amino group;

(6b) a C_{1-6} alkoxy-carbonyl-C_{1-10} alkylamino group;

(6c) a carboxy-C_{1-10} alkylamino group;

(6d) a C_{7-13} aralkyloxy-carbonylamino group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(6e) a carbamoylamino group;

(6f) a mono- or di-C_{1-6} alkyl-carbamoylamino group;

(6g) a C_{1-6} alkylsulfonylamino group;

(6h) a C_{6-14} arylsulfonylamino group optionally substituted by a C_{1-6} alkylsulfonyl group;

(6i) an aromatic heterocyclic (e.g., pyridyl, thiazolyl, oxazolyl, indolyl)-sulfonylamino group optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6}alkyl group and a mono- or di-(C_{1-6} alkyl-carbonyl)-amino group;

(6j) a mono- or di-(C_{1-6} alkyl-carbonyl)-amino group;

(6k) a C_{3-10} cycloalkyl-carbonylamino group;

(6l) a C_{6-14} aryl-carbonylamino group optionally substituted by 1 to 3 substituent(s) selected from a halogen atom, a cyano group, an optionally halogenated C_{1-6} alkyl group, a C_{1-6} alkoxy group, a carboxyl group, a C_{1-6} alkoxy-carbonyl group, an aromatic heterocyclic group (preferably tetrazolyl, oxadiazolyl), a non-aromatic heterocyclic group (preferably oxooxadiazolyl) and a carbamoyl group;

(6m) a C_{7-13} aralkyl-carbonylamino group;

(6n) a C_{8-13} arylalkenyl-carbonylamino group;

(6o) an aromatic heterocyclic (preferably furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, pyrazinyl, benzofuryl, benzothienyl, quinoxalinyl)-carbonylamino group optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group, a C_{6-14} aryl group, a C_{7-13} aralkyl group, a C_{1-6} alkoxy group, a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(6p) a nitrogen-containing heterocyclic (preferably

pyrrolidinyl, piperidinyl, piperazinyl, morpholino)-carbonylamino group optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group), a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(6q) a C_{6-14} aryl-nitrogen-containing heterocyclic (e.g., pyrrolidinyl, piperidinyl, piperazinyl, morpholino)-carbonylamino group;

(6r) a tetrahydropyranylcarbonylamino group;

(6s) a 4-oxo-4,5,6,7-tetrahydro-1-benzofuranyl-carbonylamino group;

(6t) a C_{1-6} alkoxy-carbonylamino group optionally substituted by a C_{1-6} alkoxy-carbonyl group;

(6u) a C_{6-14} aryloxy-carbonylamino group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group;

(6v) a C_{7-13} aralkyl-carbamoylamino group; or

(6w) an aromatic heterocyclic (preferably thiazolyl, oxazolyl)-carbamoylamino group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group, a C_{1-6} alkoxy-carbonyl group and a carbamoyl group; or

(7) (7a) tetrazolyl;

(7b) oxoimidazolidinyl (preferably 2-oxoimidazolidin-1-yl);

(7c) dioxoimidazolidinyl (preferably 2,4-dioxoimidazolidin-3-yl, 2,4-dioxoimidazolidin-1-yl) optionally substituted by a C_{1-6} alkyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group and a C_{1-6} alkoxy-carbonyl group;

(7d) oxopiperazinyl (preferably 3-oxopiperazin-1-yl);

(7e) dioxopiperazinyl (preferably 2,3-dioxopiperazin-1-yl, 2,5-dioxopiperazin-1-yl);

(7f) oxodihydrooxadiazolyl (preferably 5-oxo-4,5-dihydro-1,2,4-oxadiaz l-3-yl);

(7g) dioxoisoindolyl;

(7h) oxazolyl optionally substituted by a C_{1-6} alkoxy-carbonyl group;

(7i) dioxooxazolidinyl (preferably 2,4-dioxooxazolidin-5-yl) or dioxothiazolidinyl (preferably 2,4-dioxothiazolidin-5-yl), each of which is optionally substituted by a C_{1-6} alkyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group and a C_{1-6} alkoxy-carbonyl group;

(7j) 4-oxo-2-thioxo-1,3-thiazolidin-5-yl or 4-oxo-2-thioxo-1,3-oxazolidin-5-yl, each of which is optionally substituted by a C_{1-6} alkyl group optionally substituted by 1 to 3 substituent(s) selected from a carboxyl group and a C_{1-6} alkoxy-carbonyl group;

(7k) 1,3(2H,5H)-dioxo-tetrahydroimidazo[1,5-a]pyridinyl;

(7l) 1,3(2H,5H)-dioxo-10,10a-dihydroimidazo[1,5-b]isoquinolinyl; or

(7m) a C_{6-14} aryl group optionally substituted by a C_{1-6} alkoxy-carbonyl group.

[Compound E]

The aforementioned Compound D wherein

R^1 and R^2 are the same or different and each is a C_{1-10} alkyl group (preferably R^1 is isobutyl or neopentyl; R^2 is methyl);

R^3 is a C_{6-14} aryl group optionally substituted by a C_{1-6} alkyl group (R^3 is preferably 4-methylphenyl);

R^4 is an amino group; and

X is the aforementioned (3a), (3c), (3f), (3o), (3v), (4d), (5b), (6l) or (6o) [preferably (3a), (3o), (3v), (4d) or (6o)].

[Compound F]

5-(Aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid (Example 22);

5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)

nicotinic acid (Example 40);
methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate (Example 305);
{[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(2-morpholin-4-yl-2-oxoethyl)pyridin-3-yl]methyl}amine (Example 312);
methyl 3-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoate (Example 336);
N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]isoxazole-4-carboxamide (Example 350); or a salt thereof (preferably hydrochloride, trifluoroacetate, fumarate).

As a salt of compound (I), a pharmacologically acceptable salt is preferable. Examples of such salt include salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, salts with basic or acidic amino acids and the like.

Preferable examples of the 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.

Preferable examples of the salt with organic base include a salt with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, tromethamine[tris(hydroxymethyl)methylamine], tert-butylamine, cyclohexylamine, benzylamine, dicyclohexylamine, N,N-dibenzylethylenediamine and the like.

Preferable examples of the salt with inorganic acid include a salt with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like.

Preferable examples of the salt with organic acid include a salt 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.

Preferable examples of the salt with basic amino acid include a salt with arginine, lysin, ornithine and the like.

Preferable examples of the salt with acidic amino acid include a salt with aspartic acid, glutamic acid and the like.

Of the above-mentioned salts, the salt with inorganic acid and the salt with organic acid are preferable, hydrochloride, trifluoroacetate, fumarate and the like are more preferable.

A prodrug of compound (I) is a compound that converts to compound (I) due to the reaction by enzyme, gastric acid and the like under the physiological conditions in the body; that is, a compound that converts to compound (I) by enzymatic oxidation, reduction, hydrolysis and the like, and a compound that converts to compound (I) by hydrolysis and the like by gastric acid and the like. Examples of a prodrug of compound (I) include a compound wherein an amino group of compound (I) is acylated, alkylated, phosphorylated (e.g., compound where amino group of compound (I) is eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated, tert-butylated and the like); a compound wherein a hydroxy group of compound (I) is acylated, alkylated, phosphorylated, borated (e.g., a compound where a hydroxy group of compound (I) is acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated, dimethylaminomethylcarbonylated and the like); a compound wherein a carboxyl group of compound (I) is esterified or amidated (e.g., a compound where a carboxyl group of compound (I) is ethyl esterified, phenyl esterified, carboxymethyl esterified, dimethylaminomethyl esterified, pivaloyloxymethyl esterified, ethoxycarbonyloxyethyl

esterified, phthalidyl esterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterified, cyclohexyloxycarbonylethyl esterified, methylamidated and the like) and the like. These compounds can be produced from compound (I) by a method known per se.

A prodrug of compound (I) may be a compound that converts to compound (I) under physiological conditions as described in Development of Pharmaceutical Products, vol. 7, Molecule Design, 163-198, Hirokawa Shoten (1990).

The compound (I) may be labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S, ^{125}I and the like) and the like.

The compound (I) may be an anhydride or a hydrate.

The compound (I) and a prodrug thereof (hereinafter sometimes to be simply referred to as the compound of the present invention) show low toxicity and can be used as an agent for the prophylaxis or treatment of various diseases to be mentioned later for mammals (e.g., human, mouse, rat, rabbit, dog, cat, cattle, horse, swine, simian and the like) as they are or by admixing with a pharmacologically acceptable carrier and the like to give a pharmaceutical composition.

Here, various organic or inorganic carriers conventionally used as materials for pharmaceutical preparations are used as a pharmacologically acceptable carrier, which are added as excipient, lubricant, binder, disintegrant for solid preparations; and solvent, dissolution aids, suspending agent, isotonicity agent, buffer, soothing agent and the like for liquid preparations. Where necessary, additive for pharmaceutical preparations such as preservative, antioxidant, coloring agent, sweetening agent and the like can be used.

Preferable examples of the excipient include lactose, sucrose, D-mannitol, D-sorbitol, starch, pregelatinized starch, dextrin, crystalline cellulose, low-substituted hydroxypropyl cellulose, sodium carboxymethylcellulose, powdered acacia,

dextrin, pullulan, light silicic anhydride, synthetic aluminum silicate, magnesium aluminate metasilicate and the like.

Preferable examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica and the like.

Preferable examples of the binder include pregelatinized starch, saccharose, gelatin, powdered acacia, methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, crystalline cellulose, sucrose, D-mannitol, trehalose, dextrin, pullulan, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone and the like.

Preferable examples of the disintegrant include lactose, sucrose, starch, carboxymethylcellulose, calcium carboxymethylcellulose, sodium croscarmellose, sodium carboxymethyl starch, light silicic anhydride, low-substituted hydroxypropyl cellulose and the like.

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, cottonseed oil and the like.

Preferable examples of the dissolution aids include polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate, sodium acetate and the like.

Preferable examples of the suspending agent include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride, glycerol monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose and the like; polysorbates, polyoxyethylene hydrogenated castor oil; and the like.

Preferable examples of the isotonicity agent include sodium chloride, glycerol, D-mannitol, D-sorbitol, glucose and the like.

Preferable examples of the buffer include phosphate buffer, acetate buffer, carbonate buffer, citrate buffer and the like.

Preferable examples of the soothing agent include benzyl alcohol and the like.

Preferable examples of the preservative include p-oxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like.

Preferable examples of the antioxidant include sulfite, ascorbate and the like.

Preferable examples of the coloring agent include water-soluble edible tar pigments (e.g., foodcolors such as Food Color Red Nos. 2 and 3, Food Color Yellow Nos. 4 and 5, Food Color Blue Nos. 1 and 2 and the like), water insoluble lake pigments (e.g., aluminum salt of the aforementioned water-soluble edible tar pigment and the like), natural pigments (e.g., beta carotene, chlorophil, red iron oxide etc.) and the like.

Preferable examples of the sweetening agent include saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia and the like.

The dosage form of the aforementioned pharmaceutical composition is, for example, an oral agent such as tablets (inclusive of sublingual tablets and orally disintegrable tablets), capsules (inclusive of soft capsules and micro capsules), granules, powders, troches, syrups, emulsions, suspensions and the like; or a parenteral agent such as injections (e.g., subcutaneous injections, intravenous injections, intramuscular injections, intraperitoneal injecti ns, drip infusions etc.), external agents (e.g., transdermal preparations, ointments etc.), suppositories (e.g.,

rectal suppositories, vaginal suppositories etc.), pellets, nasal preparations, pulmonary preparations (inhalations), ophthalmic preparations and the like. These may be administered safely via an oral or parenteral route.

These agents may be controlled-release preparations such as rapid-release preparations and sustained-release preparations (e.g., sustained-release microcapsules).

The pharmaceutical composition can be produced according to a method conventionally used in the field of pharmaceutical preparation, such as the method described in Japan Pharmacopoeia and the like. Specific production methods of the pharmaceutical preparation are described in detail in the following.

While the content of the compound of the present invention in the pharmaceutical composition varies depending n the dosage form, dose of the compound of the present invention and the like, it is, for example, about 0.1-100 wt%.

For example, an oral agent is produced by adding, to the active ingredient, excipients (e.g., lactose, sucrose, starch, D-mannitol and the like), disintegrants (e.g., calcium carboxymethylcellulose and the like), binders (e.g., pregelatinized starch, powdered acacia, carboxymethylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone and the like), lubricants (e.g., talc, magnesium stearate, polyethylene glycol 6000 and the like) and the like, compression-molding the obtained mixture, and where necessary, coating the same using a coating base for masking of taste, enteric property or sustained release according to a method known per se.

Examples of the coating base include a sugar-coating base, a water-soluble film coating base, an enteric film coating base, a sustained release film coating base and the like.

As the sugar-coating base, sucrose may be used, if necessary, along with one or more species selected from talc,

precipitated calcium carbonate, gelatin, powdered acacia, pullulan, carnauba wax and the like.

As the water-soluble film coating base, for example, cellulose polymers such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, methylhydroxyethylcellulose and the like; synthetic polymers such as polyvinyl acetal diethylaminoacetate, aminoalkyl methacrylate copolymer E [Eudragit E, trade name, Roehm Pharma], polyvinylpyrrolidone and the like; polysaccharides such as pullulan and the like; and the like are used.

As the enteric film coating base, for example, cellulose polymers such as hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carboxymethylethylcellulose, cellulose acetate phthalate and the like; acrylic acid polymers such as methacrylic acid copolymer L [Eudragit L, trademark, Roehm Pharma], methacrylic acid copolymer LD [Eudragit L-30D55, trade name, Roehm Pharma], methacrylic acid copolymer S [Eudragit S, trade name, Roehm Pharma] and the like; natural products such as shellac and the like; and the like are used.

As the sustained release film coating base, for example, cellulose polymers such as ethylcellulose and the like; acrylic acid polymers such as aminoalkyl methacrylate copolymer RS [Eudragit RS, trade name, Roehm Pharma], ethyl acrylate-methyl methacrylate copolymer suspension [Eudragit NE, trade name, Roehm Pharma] and the like, and the like are used.

Two or more kinds of the above-mentioned coating bases may be mixed in an appropriate ratio for use. In addition, a light shielding agent such as titanium oxide, ferric oxide and the like may be used during coating.

An injection is produced by dissolving, suspending or emulsifying an active ingredient in an aqueous solvent (e.g., distilled water, physiological saline, Ringer's solution and the like) or an oily solvent (e.g., vegetable oil such as olive

oil, sesame oil, cottonseed oil, corn oil and the like, propylene glycol and the like) and the like, together with a dispersing agent (e.g., polysorbate 80, polyoxyethylene hydrogenated castor oil 60, polyethylene glycol, carboxymethylcellulose, sodium alginate and the like), preservative (e.g., methylparaben, propylparaben, benzyl alcohol, chlorobutanol, phenol and the like), isotonicity agent (e.g., sodium chloride, glycerol, D-mannitol, D-sorbitol, glucose and the like) and the like. In this step, additives such as dissolution aids (e.g., sodium salicylate, sodium acetate and the like), stabilizers (e.g., human serum albumin and the like), soothing agents (e.g., benzyl alcohol and the like) and the like may be used on demand.

The compound of the present invention shows low toxicity (e.g., acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, vascular toxicity, carcinogenic), causes fewer side effects and can be used as an agent for the prophylaxis or treatment or diagnosis of various diseases for mammals (e.g., human, cattle, horse, dog, cat, simian, mouse, rat, especially human).

The compound of the present invention has a superior peptidase inhibitory activity and can suppress peptidase-caused degradation of a physiologically active substance such as peptide hormones, cytokines, neurotransmitters and the like.

Examples of the peptide hormones include glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), GIP, growth hormone release hormone (GHRH) and the like.

Examples of the cytokines include chemokine such as RANTES and the like.

Examples of the neurotransmitters include neuropeptide Y and the like.

Examples of the peptidases include EC 3.4.11.1 (Leucyl aminopeptidase), EC 3.4.11.2 (Membrane alanine aminopeptidase), EC 3.4.11.3 (Cystinyl aminopeptidase), EC 3.4.11.4 (Tripeptide

aminopeptidase), EC 3.4.11.5 (Prolyl aminopeptidase), EC 3.4.11.6 (Aminopeptidase B), EC 3.4.11.7 (Glutamyl aminopeptidase), EC 3.4.11.9 (Xaa-Pro aminopeptidase), EC 3.4.11.10 (Bacterial leucyl aminopeptidase), EC 3.4.11.13 (Clostridial aminopeptidase), EC 3.4.11.14 (Cytosol alanyl aminopeptidase), EC 3.4.11.15 (Lysyl aminopeptidase), EC 3.4.11.16 (Xaa-Trp aminopeptidase), EC 3.4.11.17 (Tryptophanyl aminopeptidase), EC 3.4.11.18 (Methionyl aminopeptidase), EC 3.4.11.19 (D-stereospecific aminopeptidase), EC 3.4.11.20 (Aminopeptidase Ey), EC 3.4.11.21 (Aspartyl aminopeptidase), EC 3.4.11.22 (Aminopeptidase I), EC 3.4.13.3 (Xaa-His dipeptidase), EC 3.4.13.4 (Xaa-Arg dipeptidase), EC 3.4.13.5 (Xaa-methyl-His dipeptidase), EC 3.4.13.7 (Glu-Glu dipeptidase), EC 3.4.13.9 (Xaa-Pro dipeptidase), EC 3.4.13.12 (Met-Xaa dipeptidase), EC 3.4.13.17 (Non-stereospecific dipeptidase), EC 3.4.13.18 (Cytosol nonspecific dipeptidase), EC 3.4.13.19 (Membrane dipeptidase), EC 3.4.13.20 (Beta-Ala-His dipeptidase), EC 3.4.14.1 (Dipeptidyl-peptidase I), EC 3.4.14.2 (Dipeptidyl-peptidase II), EC 3.4.14.4 (Dipeptidyl-peptidase III), EC 3.4.14.5 (Dipeptidyl-peptidase IV), EC 3.4.14.6 (Dipeptidyl-dipeptidase), EC 3.4.14.9 (Tripeptidyl-peptidase I), EC 3.4.14.10 (Tripeptidyl-peptidase II), EC 3.4.14.11 (Xaa-Pro dipeptidyl-peptidase) and the like as classified by International Union of Biochemistry and Molecular Biology. As peptidase, FAPα, DPP8, DPP9 and the like can be also mentioned.

Of these, EC 3.4.14.1, EC 3.4.14.2, EC 3.4.14.4, EC 3.4.14.5, EC 3.4.14.6, EC 3.4.14.9, EC 3.4.14.10 and EC 3.4.14.11 are preferable. Especially preferred is EC 3.4.14.5 (Dipeptidyl-peptidase IV).

The compound of the present invention may concurrently have a glucagon antagonistic action or a CETP inhibitory action in additi n to a peptidase inhibitory action. When the compound of the present invention concurrently has these

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actions, the compound f the present invention is more effective as an agent for the prophylaxis or treatment of diabetes (e.g., type 1 diabetes, type 2 diabetes, gestational diabetes mellitus etc.) and hyperlipidemia (e.g., hypertriglyceridemia, hypercholesteremia, hypoHDLemia, postprandial hyperlipidemia etc.).

The compound of the present invention is useful as an agent for the prophylaxis or treatment of diabetes (e.g., type 1 diabetes, type 2 diabetes, gestational diabetes and the like); an agent for the prophylaxis or treatment of hyperlipidemia (e.g., hypertriglyceridemia, hypercholesterolemia, hypoHDLemia, postprandial hyperlipidemia and the like); an agent for the prophylaxis or treatment f arteriosclerosis; an agent for the prophylaxis or treatment of impaired glucose tolerance [IGT]; an insulin secretagogue; and an agent for preventing progress of impaired glucose tolerance into diabetes.

For diagnostic criteria of diabetes, Japan Diabetes Society reported new diagnostic criteria in 1999.

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 h 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 h level (glucose concentration of intravenous plasma) of less than 140 mg/dl" (normal type) is called a "borderline type".

In addition, ADA (American Diabetes Association)

reported new diagnostic criteria of diabetes in 1997 and WHO in 1998.

According to these reports, diabetes is a condition showing a fasting blood glucose level (glucose concentration f intravenous plasma) of not less than 126 mg/dl and a 75 g oral glucose tolerance test 2 h level (glucose concentration of intravenous plasma) of not less than 200 mg/dl.

According to the above-mentioned reports, impaired glucose tolerance is a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of less than 126 mg/dl and a 75 g oral glucose tolerance test 2 h 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 75g oral glucose tolerance test 2 h level (glucose concentration of intravenous plasma) of less than 140 mg/dl is called IFG (Impaired Fasting Glycemia).

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.

The compound of the present invention can be also used as an agent for the prophylaxis or treatment of, for example, diabetic complications [e.g., neuropathy, nephropathy, retinopathy, cataract, macroangiopathy, osteopenia,

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hyperosmolar diabetic coma, infectious disease (e.g., respiratory infection, urinary tract infection, gastrointestinal infection, dermal soft tissue infections, inferior limb infection and the like), diabetic gangrene, xerostomia, hypacusis, cerebrovascular disorder, peripheral blood circulation disorder and the like], obesity, osteoporosis, cachexia (e.g., cancerous cachexia, tuberculous cachexia, diabetic cachexia, blood disease cachexia, endocrine disease cachexia, infectious disease cachexia or cachexia due to acquired immunodeficiency syndrome), fatty liver, hypertension, polycystic ovary syndrome, kidney disease (e.g., diabetic nephropathy, glomerular nephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, end stage kidney disease and the like), muscular dystrophy, myocardial infarction, angina pectoris, cerebrovascular accident (e.g., cerebral infarction, cerebral apoplexy), Alzheimer's disease, Parkinson's syndrome, anxiety, dementia, insulin resistance syndrome, Syndrome X, metabolic syndrome, hyperinsulinemia, hyperinsulinemia-induced sensory disorder, tumor (e.g., leukemia, breast cancer, prostatic cancer, skin cancer and the like), irritable bowel syndrome, acute or chronic diarrhea, inflammatory diseases (e.g., chronic rheumatoid arthritis, spondylitis deformans, osteoarthritis, lumbago, gout, postoperative or traumatic inflammation, tumentia, neuralgia, pharyngolaryngitis, cystitis, hepatitis (inclusive of nonalcoholic steatohepatitis), pneumonia, pancreatitis, enteritis, inflammatory bowel diseases (including inflammatory disease of large intestine), ulcerative colitis, gastric mucosal injury (inclusive of gastric mucosal injury caused by aspirin) and the like), small intestine mucous membrane trauma, malabsorption, testis function disorder, visceral obesity syndrome and the like.

The compound of the present invention can be also used for decreasing visceral fat, suppressing visceral fat

accumulation, improving glycometabolism, improving lipid metabolism, suppressing production of oxidized LDL, improving lipoprotein metabolism, improving coronary artery metabolism, prophylaxis and treatment of cardiovascular complications, prophylaxis and treatment of heart failure complications, lowering blood remnant, prophylaxis and treatment of anovulation, prophylaxis and treatment of hypertrichosis, prophylaxis and treatment of hyperandrogenemia, improving pancreatic (β cell) function, regeneration of pancreatic (β cell), promotion of pancreatic (β cell) regeneration, appetite control and the like.

The compound of the present invention can be also used for secondary prophylaxis and prevention of progression of the above-mentioned various diseases (e.g., cardiovascular event such as myocardial infarction and the like).

The compound of the present invention is a glucose dependent insulin secretagogue that selectively promotes insulin secretion in hyperglycemic patients (e.g., patients showing fasting blood glucose level of not less than 126 mg/dl or 75 g oral glucose tolerance test (75 g OGTT) 2 h level of not less than 140 mg/dl and the like). Therefore, the compound of the present invention is useful as a safe agent for the prophylaxis or treatment of diabetes with a low risk of vascular complications, hypoglycemia induction and the like caused by insulin.

The compound of the present invention is also useful as a therapeutic agent for diabetes with sulfonylurea secondary failure and affords a superior insulin secretion effect and a hypoglycemic effect for diabetic patients for whom sulfonylurea compounds and fast-acting insulin secretagogues fail to provide an insulin secretion effect, and therefore, fail to provide a sufficient hypoglycemic effect.

As the sulfonylurea compound here, a compound having a sulfonylurea skeleton or a derivative thereof, such as

tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride, glipizide, glybuzole and the like can be mentioned.

As the fast-acting insulin secretagogue, a compound that promotes insulin secretion from pancreatic β cell in the same manner as a sulfonylurea compound, though it does not have a sulfonylurea skeleton, such as glinide compounds (e.g., repaglinide, senaglinide, nateglide, mitiglinide, a calcium salt hydrate thereof etc.), and the like, can be mentioned.

While the dose of the compound of the present invention varies depending on the administration subject, administration route, target disease, condition and the like, the compound of the present invention as an active ingredient is generally given in a single dose of about 0.01-100 mg/kg body weight, preferably 0.05-30 mg/kg body weight, more preferably 0.1-10 mg/kg body weight, in the case of, for example, oral administration to adult diabetic patients. This dose is desirably given 1 to 3 times a day.

The compound of the present invention can be used in combination with drugs such as a therapeutic agent of diabetes, a therapeutic agent of diabetic complications, an antihyperlipemic agent, an antihypertensive agent, an antiobestic agent, a diuretic, a chemotherapeutic agent, an immunotherapeutic agent, an antithrombotic agent, a therapeutic agent of osteoporosis, an antidementia agent, an agent for improving erectile dysfunction, a therapeutic agent for incontinentia or pollakiuria, a therapeutic agent for dysurea and the like (hereinafter to be referred to as a combination drug). In this case, the timing of administration of the compound of the present invention and a combination drug is not limited. These may be simultaneously administered to an administration subject or administered in a staggered manner. Moreover, the compound of the present invention and a combination drug may be administered as two kinds of

preparations each containing an active ingredient, or may be administered as a single preparation containing both active ingredients.

The dose of the combination drug can be determined as appropriate based on the dose clinically employed. The proportion of the compound of the present invention and combination drug can be appropriately determined depending on the administration subject, administration route, target disease, condition, combination and the like. When, for example, the administration subject is human, a combination drug is used in an amount of 0.01-100 parts by weight per 1 part by weight of the compound of the present invention.

As the therapeutic agent for diabetes, insulin preparations (e.g., animal insulin preparations extracted from the pancreas of bovine and pig; human insulin preparations genetically synthesized using *Escherichia coli* or yeast; zinc insulin; protamine zinc insulin; fragment or derivative of insulin (e.g., INS-1 etc.), oral insulin preparation and the like), insulin sensitizers (e.g., pioglitazone or a salt thereof (preferably hydrochloride), rosiglitazone or a salt thereof (preferably maleate), Reglixane (JTT-501), GI-262570, Netoglitazone (MCC-555), YM-440, DRF-2593, BM-13.1258, KRP-297, R-119702, Rivoglitazone (CS-011), FK-614, compounds described in WO99/58510 (e.g., (E)-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-4-phenylbutyric acid), compounds described in WO01/38325, Tesaglitazar (AZ-242), Ragaglitazar (NN-622), Muraglitazar (BMS-298585), ONO-5816, BM-13-1258, LM-4156, MBX-102, LY-519818, MX-6054, LY-510929, Balaglitazone (NN-2344), T-131 or a salt thereof, THR-0921 etc.), PPARγ agonist, PPARγ antagonist, PPARγ/α dual agonist, α-glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate etc.), biguanides (e.g., phenformin, metformin, buformin or salts thereof (e.g., hydrochloride, fumarate, succinate) etc.), insulin secretagogues [sulfonylurea (e.g.,

tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glycl pyramide, glimepiride, glipizide, glybuzole etc.), repaglinide, senaglinide, nateglide, mitiglinide or calcium salt hydrate thereof], GPR40 agonist, GLP-1 receptor agonists [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 agonists (e.g., pramlintide etc.), phosphotyrosine phosphatase inhibitors (e.g., sodium vanadate etc.), dipeptidyl peptidase IV inhibitors (e.g., NVP-DPP-278, PT-100, P32/98, LAF-237, P93/01, TS-021, MK-431, BMS-477118 etc.), β3 agonist (e.g., CL-316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085, AZ40140 etc.), gluconeogenesis inhibitors (e.g., glycogen phosphorylase inhibitor, glucose-6-phosphatase inhibitor, glucagon antagonist etc.), SGLT (sodium-glucose cotransporter) inhibitors (e.g., T-1095 etc.), 11β-hydroxysteroid dehydrogenase inhibitors (e.g., BVT-3498 etc.), adiponectin or agonist thereof, IKK inhibitors (e.g., AS-2868 etc.), leptin resistance improving drugs, somatostatin receptor agonists (compounds described in WO01/25228, WO03/42204, WO98/44921, WO98/45285, WO99/22735 etc.), glucokinase activators (e.g., Ro-28-1675) and the like can be mentioned.

Examples of the therapeutic agent for diabetic complications include aldose reductase inhibitors (e.g., Tolrestat, Epalrestat, Zenarestat, Zopolrestat, Minalrestat, Fidarestat (SNK-860), CT-112 etc.), neurotrophic factors and increasing drugs thereof (e.g., NGF, NT-3, BDNF, neurotrophin production-secretion promoters described in WO01/14372 (e.g., 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-[3-(2-methylphenoxy)propyl]oxazole etc.) and the like), neuranagenesis stimulators (e.g., Y-128 etc.), PKC inhibitors (e.g., ruboxistaurin mesylate; LY-333531 etc.), AGE inhibitors (e.g., ALT946, pimagedine, pyratoxanthine, N-phenacylthiazolium bromide (ALT766), ALT-711, EXO-226, Pyridorin, Pyridoxamine etc.), reactive oxygen scavengers (e.g., thioctic acid etc.),

cerebral vasodilators (e.g., tiapride, mexiletine etc.), somatostatin receptor agonists (BIM23190) and apoptosis signal regulating kinase-1 (ASK-1) inhibitors.

Examples of the antihyperlipemic agent include statin compounds which are cholesterol synthesis inhibitors (e.g., cerivastatin, pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, itavastatin, rosuvastatin, pitavastatin and salts thereof (e.g., sodium salt, calcium salt) etc.), squalene synthase inhibitors (e.g., compounds described in WO97/10224, such as N-[[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetic acid etc.), fibrate compounds (e.g., bezafibrate, clofibrate, simfibrate, clinofibrate etc.), ACAT inhibitors (e.g., Avasimibe, Eflucimibe etc.), anion exchange resins (e.g., colestyramine etc.), probucol, nicotinic acid drugs (e.g., nicomol, niceritrol and the like), ethyl icosapentate, plant sterols (e.g., soysterol, γ-oryzanol etc.) and the like.

Examples of the antihypertensive agent include angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril etc.), angiotensin II antagonists (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 etc.), calcium antagonists (e.g., manidipine, nifedipine, amlodipine, efonidipine, nicardipine etc.), potassium channel openers (e.g., levcromakalim, L-27152, AL 0671, NIP-121 etc.), Clonidine and the like.

Examples of the antiobestic agent include antiobestic agents acting on the central nervous system (e.g., Dexfenfluramine, fenfluramine, phentermine, Sibutramine, amfepramone, dexamphetamine, Mazindol, phenylpropanolamine, clobenzorex; MCH receptor antagonists (e.g., SB-568849; SNAP-

7941; compounds encompassed in WO01/82925 and WO01/87834 etc.); neuropeptide Y antagonists (e.g., CP-422935 etc.); cannabinoid receptor antagonists (e.g., SR-141716, SR-147778 etc.); ghrelin antagonist; 11β-hydroxysteroid dehydrogenase inhibitors (e.g., BVT-3498 etc.) and the like), pancreatic lipase inhibitors (e.g., orlistat, ATL-962 etc.), β3 agonists (e.g., CL-316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085, AZ40140 etc.), peptidic anorexiants (e.g., leptin, CNTF (Ciliary Neurotropic Factor) etc.), cholecystokinin agonists (e.g., lintitript, FPL-15849 etc.), feeding deterrent (e.g., P-57 etc.) and the like.

Examples of the diuretic include xanthine derivatives (e.g., sodium salicylate and theobromine, calcium salicylate and theobromine etc.), thiazide preparations (e.g., ethiazide, cyclopenthiazide, trichloromethyazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, polythiazide, methyclothiazide etc.), antialdosterone preparations (e.g., spironolactone, triamterene etc.), carbonate dehydratase inhibitors (e.g., acetazolamide and the like), chlorobenzenesulfonamide preparations (e.g., chlortalidone, mefruside, indapamide etc.), azosemide, isosorbide, etacrynic acid, piretanide, bumetanide, furosemide and the like.

Examples of the chemotherapeutic agent include alkylation agents (e.g., cyclophosphamide, ifosfamide etc.), metabolic antagonists (e.g., methotrexate, 5-fluorouracil or its derivative, etc.), anti-cancer antibiotics (e.g., mitomycin, adriamycin etc.), plant-derived anti-cancer agents (e.g., vincristin, vindesine, taxol etc.), cisplatin, carboplatin, etoposide and the like. Of these, furtulon and neofurtulon, which are 5-fluorouracil derivatives, and the like are preferable.

Examples of the immunotherapeutic agent include microorganism or bacterial components (e.g., muramyl dipeptide

derivative, picibanil etc.), polysaccharides having immunity potentiating activity (e.g., lentinan, sizofiran, krestin etc.), cytokines obtained by genetic engineering techniques (e.g., interferon, interleukin (IL) etc.), colony stimulating factors (e.g., granulocyte colony stimulating factor, erythropoietin etc.) and the like, with preference given to interleukins such as IL-1, IL-2, IL-12 and the like.

Examples of the antithrombotic agent include heparin (e.g., heparin sodium, heparin calcium, dalteparin sodium etc.), warfarin (e.g., warfarin potassium etc.), anti-thrombin drugs (e.g., aragatroban etc.), thrombolytic agents (e.g., urokinase, tisokinase, alteplase, nateplase, monteplase, pamiteplase etc.), platelet aggregation inhibitors (e.g., ticlopidine hydrochloride, cilostazol, ethyl icosapentate, beraprost sodium, sarpogrelate hydrochloride etc.) and the like.

Examples of the therapeutic agent of osteoporosis include alfacalcidol, calcitriol, elcatonin, calcitonin salmon, estriol, ipriflavone, pamidronate disodium, alendronate sodium hydrate, incadronate disodium and the like.

Examples of the antidementia agent include tacrine, donepezil, rivastigmine, galanthamine and the like.

Examples of the agent for improving erectile dysfunction include apomorphine, sildenafil citrate and the like.

Examples of the therapeutic agent for incontinentia or pollakiuria include flavoxate hydrochloride, oxybutynin hydrochloride, propiverine hydrochloride and the like.

Examples of the therapeutic agent for dysurea include acetylcholine esterase inhibitors (e.g., distigmine) and the like can be mentioned.

Furthermore, drugs having a cachexia-improving action established in animal models and clinical situations, such as cyclooxygenase inhibitors (e.g., Indometacin etc.), Progesterone derivatives (e.g., Megesterol acetate),

glucosteroid (e.g., dexamethasone etc.), metoclopramide agents, tetrahydrocannabinol agents, fat metabolism improving agents (e.g., eicosapentaenoic acid etc.), growth hormones, IGF-1, or antibodies to a cachexia-induced factor such as TNF-α, LIF, IL-6, Oncostatin M and the like, can be used in combination with the compound of the present invention.

The combination drug is preferably an insulin preparation, an insulin sensitizer, an α-glucosidase inhibitor, a biguanide, an insulin secretagogue (preferably sulfonylurea) and the like.

Two or more of the above-mentioned combination drugs can be used in combination in an appropriate ratio. Preferable combinations in the case of using two or more combination drugs are, for example, as shown in the following.

1) an insulin secretagogue (preferably sulfonylurea) and an α-glucosidase inhibitor;

2) an insulin secretagogue (preferably sulfonylurea) and a biguanide;

3) an insulin secretagogue (preferably sulfonylurea), a biguanide and an α-glucosidase inhibitor;

4) an insulin sensitizer and an α-glucosidase inhibitor;

5) an insulin sensitizer and a biguanide;

6) an insulin sensitizer, a biguanide and an α-glucosidase inhibitor.

When the compound of the present invention is used in combination with a combination drug, the amount thereof can be reduced within a safe range in consideration of counteraction of these agents. Particularly, the dose of an insulin sensitizer, an insulin secretagogue (preferably sulfonylurea) and a biguanide can be reduced as compared with the normal dose. Therefore, an adverse effect, which may be caused by these agents, can be prevented safely. In addition, the dose of the therapeutic agent of diabetic complications, antihyperlipemic agent and antihypertensive agent can be

reduced whereby an adverse effect, which may be caused by these agents, can be prevented effectively.

Hereinafter the production methods of the compound of the present invention are explained.

The compound of the present invention can be produced according to a method known *per se*, such as a method to be described in detail in the following, or an analogous method thereto.

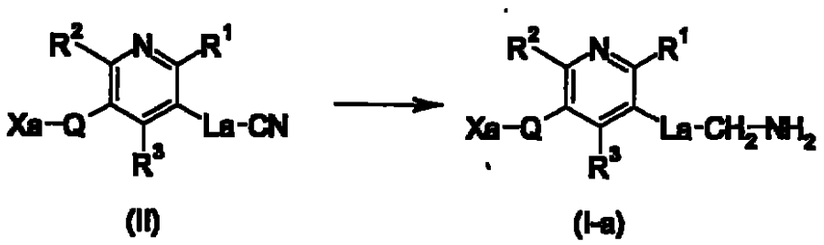
Compound (I-a), which is a compound of the formula (I) wherein L is La-CH_2-, (wherein La is a bond or a divalent chain hydrocarbon group), X is Xa (wherein Xa is a hydrogen atom, a nitro group, an acyl group, a substituted hydroxy group, an optionally substituted thiol group, an optionally substituted amino group or an optionally substituted cyclic group), and R^4 is an amino group, can be produced according the following Method A or an analogous method thereto.

As the "divalent chain hydrocarbon group" for La, those similar to the "divalent chain hydrocarbon group" exemplarily recited for the aforementioned L can be mentioned. La is preferably a bond or C_{1-9} alkylene group.

In addition, as the "acyl group", "substituted hydroxy group", "optionally substituted thiol group", "optionally substituted amino group" and "optionally substituted cyclic group", each for Xa, those exemplarily recited for the aforementioned X can be used.

When Xa is an ethoxycarbonyl group, then Q is preferably a divalent chain hydrocarbon group

[Method A]



(II) (I-a)

wherein the symbols in the formula are as defined above.

In this method, compound (II) is subjected to a reduction reaction to give compound (I-a).

The reduction reaction is carried out in the presence of a reducing agent, in a solvent that does not adversely influence the reaction, according a conventional method.

As the reducing agent, for example, metal hydrides such as sodium bis(2-methoxyethoxy)aluminum hydride, diisobutylaluminum hydride and the like; metal hydride complexes such as sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride, sodium aluminum hydride and the like; and the like can be mentioned.

The amount of the reducing agent to be used is generally 0.1 to 20 equivalents relative to compound (II).

As the solvent that does not adversely influence the reaction, for example, alcohols such as methanol, ethanol, propanol, 2-propanol, 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-butylmethyl 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 dimethylformamide, dimethylacetamide, N-methylpyrrolidone and the like, can be used. These solvents may be used in a mixture of two or more kinds thereof mixed at an appropriate ratio.

The reaction temperature is generally -70 to 150°C, preferably -20 to 100°C.

The reaction time is generally 0.1 to 100 hrs, preferably 0.1 to 40 hrs.

The reduction reaction can be also carried out in the presence of a metal catalyst such as palladium-carbon,

palladium black, 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 to 1000 equivalents, preferably 0.01 to 100 equivalents relative to compound (II).

As the hydrogen source, for example, hydrogen gas, formic acid, formic acid amine salt, phosphinic acid salt, hydrazine and the like can be mentioned.

As the solvent that does not adversely influence the reaction, those used in the aforementioned reduction reaction using the reducing agent can be mentioned.

The reaction temperature and the reaction time are the same as those for the aforementioned reduction reaction using the reducing agent.

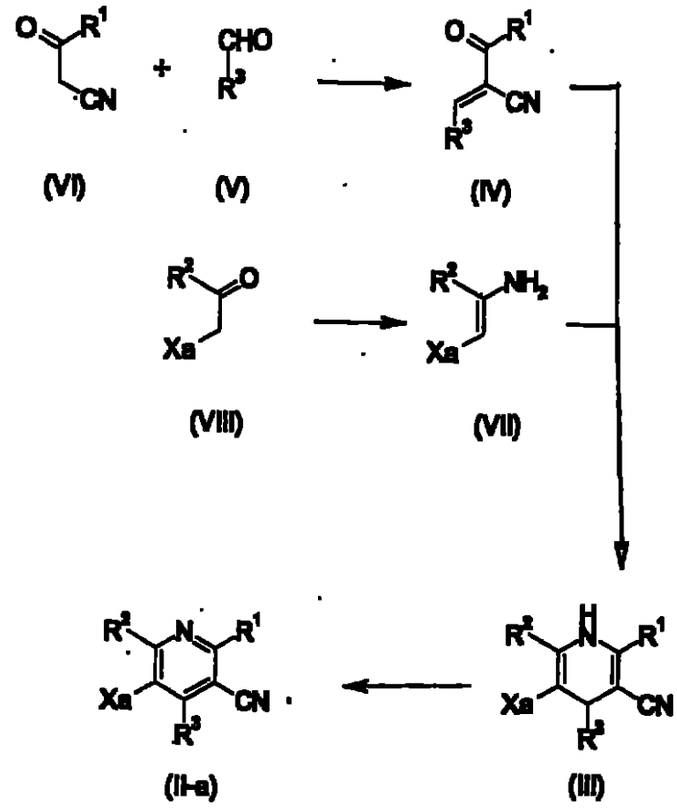
This reaction may be carried out in the presence of ammonia (e.g., aqueous ammonia, ammonia-ethanol and the like) where necessary. By the reaction in the presence of ammonia, the side reaction can be suppressed and compound (I-a) can be produced in a high yield.

Compound (I-a) thus obtained can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

Compound (II) used as the starting compound in the above-mentioned Method A, can be produced according to a method known per se.

For example, compound (II-a), which is a compound of the formula (II) wherein Q and La are a bond and Xa is an acyl group, can be produced according to the following Method B.

[Method B]



(VI) (V) (IV) (VIII) (VII) (III) (II-a)

wherein the symbols in the formula are as defined above.

Compound (II-a) can be produced according to a method known *per se*; for example, by reacting compound (III) and a oxidant such as diluted nitric acid, diammonium cerium nitrate and the like, in a solvent that does not adversely influence the reaction such as 1,4-dioxane, acetone and the like.

Compound (III) can be produced according to a method known *per se*; for example, from compound (IV) and compound (VII) according to a pyridine synthetic method by Hantzch as described in "Shin Jikken Kagaku Kouza (The Chemical Society of Japan ed.), Vol. 14, Synthesis and Reaction of Organic Compound IV, Maruzen (1978), page 2057, or a method analogous thereto.

Compound (IV) can be produced according to a method known *per se*, for example, by subjecting compound (VI) and compound (V) to the known Knoevenagel method.

Compound (VII) can be produced according to a method known *per se*, for example, from compound (VIII) according to the method described in Synthesis (1999), vol. 11, pages 1951-

1960; Journal of Chemical Society Perkin Transactions 1, (2002), pages 1663-1671 and the like, or a method analogous thereto.

The aforementioned compound (V), compound (VI) and compound (VIII) can be produced according to a method known per se.

Compound (I-b), which is a compound of the formula (I) wherein R^4 is an amino group mono- or di-substituted by C_{1-10} alkyl group, can be produced by subjecting compound (I-c), which is a compound of the formula (I) wherein R^4 is an amino group, to an alkylation reaction.

This reaction is carried out (1) in the presence of base where necessary, using an alkylating agent in a solvent that does not adversely influence the reaction, or (2) in the presence of reducing agent where necessary, using a carbonyl compound in a solvent that does not adversely influence the reaction, according to a method known.

As the alkylating agent here, for example, C_{1-10} alkylhalide, C_{1-10} alkyl sulfonate and the like can be mentioned.

As the carbonyl compound, for example, aldehydes, ketones and the like can be mentioned.

The amount of the alkylating agent and the carbonyl compound to be used are preferably about 1 to about 5 equivalents relative to compound (I-c).

As the base, for example, alkali metal salts such as sodium hydroxide, potassium carbonate and the like; amines such as pyridine, triethylamine and the like; metal hydrides such as sodium hydride and the like; alkali metal alkoxides such as sodium methoxide, potassium t-butoxide and the like, and the like can be mentioned.

The amount of the base to be used is preferably about 1 to about 5 equivalents relative to compound (I-c).

As the reducting agent, for example, metal hydrides such

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as diisobutylaluminum hydride and the like; metal hydride complexes such as sodium cyanoborohydride and the like; and the like can be mentioned.

The amount of the reducting agent to be used is generally 0.1 to 20 equivalents relative to compound (I-c).

The reaction using the aforementioned carbonyl compound can be also carried out in the presence of a metal catalyst such as palladium-carbon and the like and a hydrogen source, without the reducing agent, in a solvent that does not adversely influence the reaction.

The amount of the metal catalyst to be used is preferably 0.01 to 100 equivalents relative to compound (I-c).

As the hydrogen source, for example, hydrogen gas, formic acid, formic acid amine salt and the like can be mentioned.

As 'the solvent that does not adversely influence the reaction' used for the alkylation reaction, for example, aromatic hydrocarbons such as toluene and the like; ethers such as tetrahydrofuran and the like; halogenated hydrocarbons such as chloroform and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like, and the like can be mentioned. These solvents may be used in a mixture thereof mixed at an appropriate ratio.

In the alkylation reaction, the reaction temperature is preferably about -10 to about 100°C.

In the alkylation reaction, the reaction time is generally about 0.5 to about 20 hrs.

Compound (I-b) thus obtained can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

Upon producing the compound of the present invention,

when the starting compound has amino group, carboxyl group, hydroxy group or carbonyl group as a substituent, a protecting group generally used in peptide chemistry and the like may be introduced into these groups. By removing the protecting group as necessary after the reaction, the objective compound can be obtained.

The amino-protecting group includes, for example, formyl group, C_{1-6} alkyl-carbonyl group (e.g., acetyl, propionyl and the like), C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl and the like), benzoyl group, C_{7-13} aralkyl-carbonyl group (e.g., benzylcarbonyl and the like), C_{7-13} aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl and the like), trityl group, phthaloyl group, N,N-dimethylaminomethylene group, silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl and the like), C_{2-6} alkenyl group (e.g., 1-allyl and the like) and the like. These groups are optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like), C_{1-6} alkoxy group (e.g., methoxy, ethoxy, propoxy and the like), nitro group and the like.

The carboxy-protecting group is, for example, C_{1-6} alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and the like), C_{7-13} aralkyl group (e.g., benzyl and the like), phenyl group, trityl group, silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl and the like), C_{2-6} alkenyl group (e.g., 1-allyl and the like) and the like. These groups are optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like), C_{1-6} alkoxy group (e.g., methoxy, ethoxy, propoxy and the like) or nitro group and the like.

The hydroxy-protecting group is, for example, C_{1-6} alkyl

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group (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and the like), phenyl group, trityl group, C_{7-13} aralkyl group (e.g., benzyl and the like), formyl group, C_{1-6} alkyl-carbonyl group (e.g., acetyl, propionyl and the like), benzoyl group, C_{7-13} aralkyl-carbonyl group (e.g., benzylcarbonyl and the like), 2-tetrahydropyranyl group, 2-tetrahydrofuranyl group, silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl and the like), C_{2-6} alkenyl group (e.g., 1-allyl and the like) and the like. These groups are optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like), C_{1-6} alkyl group (e.g., methyl, ethyl, propyl and the like), C_{1-6} alkoxy group (e.g., methoxy, ethoxy, propoxy and the like) or nitro group and the like.

The carbonyl-protecting group is, for example, cyclic acetal (e.g., 1,3-dioxane and the like), non-cyclic acetal (e.g., di-C_{1-6} alkyl acetal and the like) and the like.

Introduction and removal of these protecting groups can follow a method known *per se*, for example, a method described in Protective Groups in Organic Synthesis, John Wiley and Sons (1980) and the like. For example, employed is a method using acid, base, UV light, hydrazine, phenyl hydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, trialkylsilyl halide (e.g., trimethylsilyl iodide, trimethylsilyl bromide and the like) and the like, reduction and the like.

When the starting compound can form a salt upon producing the compound of the present invention, the compound in the form of a salt may be used. As such salt, those exemplarily recited above for the salt of compound (I) can be used.

When compound (I) contains an optical isomer, a stereoisomer, a positional isomer or a rotational isomer, these

are also encompassed in compound (I), and can be obtained as a single product according to a synthetic method and separation method known *per se*. For example, when compound (I) has an optical isomer, an optical isomer resolved from this compound is also encompassed in compound (I).

The optical isomer can be produced by 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 and the like.

1) Fractional recrystallization method

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 and the like) is formed, which is separated by a fractional recrystallization method, and a free optical isomer is obtained by a neutralization step where desired.

2) Chiral column method

A racemate or a salt thereof is applied to a column for separation of an optical isomer (chiral column) to allow separation. In the case of a liquid chromatography, for example, a mixture of an optical isomer is applied to a chiral column such as ENANTIO-OVM (manufactured by Tosoh Corporation) or CHIRAL series (manufactured by Daicel Chemical Industries, Ltd.) and the like, and developed with water, various buffers (e.g., phosphate buffer) and organic solvents (e.g., ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine and the like) 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

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(manufactured by GL Sciences Inc.) and the like is used to allow separation.

3) Diastereomer method

A racemic mixture is prepared into a diastereomeric mixture by chemical reaction with an optically active reagent, which is prepared into a single substance by a typical separation means (e.g., fractional recrystallization, chromatography method and the like) and the like, and 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) contains hydroxy group or primary or secondary amino group in a molecule, the compound and an optically active organic acid (e.g., MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid], (-)-menthoxyacetic acid and the like) and the like are subjected to condensation reaction to give an ester form diastereomer or amide form diastereomer, respectively. When compound (I) has a carboxyl group, this compound and an optically active amine or an optically alcohol reagent are subjected to condensation reaction to give an amide form diastereomer or ester form diastereomer, respectively. The separated diastereomer is converted to an optical isomer of the original compound by acidic hydrolysis or basic hydrolysis reaction.

The compound (I) may be in the form of a crystal.

The crystal of compound (I) (hereinafter sometimes to be referred to as crystal of the present invention) can be produced by crystallization of compound (I) by a crystallization method known per se.

Examples of the crystallization method include crystallization from a solution, crystallization from vapor, crystallization from a molten form and the like.

The "crystallization from a solution" is typically a method including shifting a non-saturated state to

supersaturated state by varying factors involved in solubility of compounds (solvent composition, pH, temperature, ionic strength, redox state etc.) or the amount of solvent. To be specific, for example, concentration method, annealing method, reaction method (diffusion method, electrolysis method), hydrothermal growth method, fusing agent method and the like can be mentioned. Examples of the solvent to be used include aromatic hydrocarbons (e.g., benzene, toluene, xylene etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane etc.), ethers (e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane etc.), nitriles (e.g., acetonitrile etc.), ketones (e.g., acetone etc.), sulfoxides (e.g., dimethyl sulfoxide etc.), acid amides (e.g., N,N-dimethylformamide and the like), esters (e.g., ethyl acetate etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol etc.), water and the like. These solvents are used alone or in combination of two or more at a suitable ratio (e.g., 1:1 to 1:100 (volume ratio)).

The "crystallization from vapor" is, for example, vaporization method (sealed tube method, gas stream method), gas phase reaction method, chemical transportation method and the like.

The "crystallization from a molten form" is, for example, normal freezing method (Czockralski method, temperature gradient method, Bridgman method), zone melting method (zone leveling method, floating zone method), special growth method (VLS method, liquid phase epitaxy method) and the like.

Preferable examples of the crystallization method include a method including dissolving compound (I) in a suitable solvent (e.g., alcohols such as methanol, ethanol etc., and the like) at a temperature of 20 to 120°C and cooling the resulting solution to a temperature not higher than the

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temperature of dissolution (e.g., 0 to 50°C, preferably 0 to 20°C) and the like.

The thus-obtained crystals of the present invention can be isolated by, for example, filtration and the like.

In the present specification, the melting point refers to that measured using, for example, micromelting point measuring apparatus (Yanako, MP-500D or Buchi, B-545) or DSC (differential scanning calorimetry) device (SEIKO, EXSTAR6000) and the like.

In general, melting points vary depending on measurement apparatuses, measurement conditions and the like. The crystal in the present specification may show a different melting point described in the present specification, as long as it is within general error range.

The crystal of the present invention is superior in physicochemical properties (e.g., melting point, solubility, stability etc.) and biological properties (e.g., pharmacokinetics (absorption, distribution, metabolism, excretion), efficacy expression etc.), and is extremely useful as a pharmaceutical agent.

Examples

The present invention is explained in more detail by the following Examples, Experimental Examples and Formulation Examples. These do not limit the present invention and the present invention can be modified within the range that does not deviate from the scope of the invention.

Abbreviations in the Examples have the following meanings:

s : singlet, d: doublet, t: triplet, q: quartet,
m: multiplet, brs: broad singlet,
J: coupling constant, 4-Me-Phenyl: 4-methylphenyl,
4-F-Phenyl: 4-fluorophenyl,
2,6-di-F-Phenyl: 2,6-difluorophenyl.

In the Examples, room temperature means the temperature of 1 to 30°C, and % means percent by weight, unless mentioned otherwise.

Example 1

methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate

1) A suspension of sodium hydride (60% in oil, 8.0 g, 0.2 mol) in tetrahydrofuran (80 mL) was heated under reflux with stirring vigorously. A mixture of methyl isovalerate (11.6 g, 0.1 mol), acetonirtile (10.5 mL, 0.2 mol) and tetrahydrofuran (25 mL) was added dropwise to the obtained suspension over 30 min., and the mixture was heated under reflux for 5 hrs. The reaction mixture was allowed to cool to room temperature, and 2-propanol (5 mL) was added thereto. The mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in water (100 mL) and washed successively with hexane and a mixed solution of hexane-diethyl ether. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with diethyl ether. The extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 5-methyl-3-oxohexanenitrile (12.6 g, yield 100%) as a yellow oil. The obtained yellow oil was used in the next step without further purification.

^{1}H-NMR ($CDCl_3$) δ:0.96 (6H, d, J = 6.6 Hz), .2.05-2.30 (1H, m), 2.50 (2H, d, J = 7.0 Hz), 3.43 (2H, s).

2) A mixture of 5-methyl-3-oxohexanenitrile (5.0 g, 40 mmol), p-tolualdehyde (4.8 g, 40 mmol), piperidine (0.34 g, 4.0 mmol), acetic acid (0.48 g, 8.0 mmol) and toluene (200 mL) was heated under reflux for 12 hrs. using a Dean-Stark trap. The reacti n mixture was allowed to cool to room temperature, washed with saturated brine and dried over anhydrous magnesium sulfate.

The solvent was evaporated under reduced pressure and the obtained residue was dissolved in methanol (50 mL). Methyl 3-aminocrotonate (4.6 g, 40 mmol) was added thereto and the mixture was heated under reflux for 6 hrs. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give methyl 5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (7.45 g, yield 57%) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ:0.93 (3H, d, J = 6.6 Hz), 0.98 (3H, d, J = 6.6 Hz), 1.80-2.00 (1H, m), 2.10-2.35 (2H, m), 2.30 (3H, s), 2.36 (3H, s), 3.58 (3H, s), 4.57 (1H, s), 5.68 (1H, brs), 7.00-7.20 (4H, m).

3) Methyl 5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (7.3 g, 22.5 mmol) was dissolved in 1,4-dioxane (20 mL), and 2N nitric acid (100 mL) was added thereto and the mixture was stirred at 70°C for 1 hr. While stirring in an ice bath, ethyl acetate (100 mL) and 2N aqueous sodium hydroxide solution (100 mL) were added thereto. The aqueous layer was separated and extracted with ethyl acetate. The organic layer and the extract were combined, and the mixture was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give methyl 5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (5.94 g, yield 82%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:1.01 (6H, d, J = 6.6 Hz), 2.20-2.35 (1H, m), 2.41 (3H, s), 2.63 (3H, s), 2.95 (2H, d, J = 7.4 Hz), 3.60 (3H, s), 7.20-7.30 (4H, m).

4) A mixture of methyl 5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.00 g, 3.10 mmol), Raney-nickel (4 mL), 25% aqueous ammonia (6 mL), tetrahydrofuran (15 mL), methanol (45 mL) was stirred in a sealed tube under 0.5 MPa

hydrogen atmosphere at room temperature for 6 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 10% aqueous potassium carbonate solution. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.97 g, yield 95%) as yellow crystals.

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.6 Hz), 1.39 (2H, brs), 2.15-2.30 (1H, m), 2.39 (3H, s), 2.53 (3H, s), 2.80 (2H, d, J = 7.2 Hz), 3.50 (3H, s), 3.66 (2H, s), 7.11 (2H, d, J = 8.0 Hz), 7.21 (2H, d, J = 8.0 Hz).

melting point: 56-57°C

Example 2

5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid dihydrochloride

1) To a solution of methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.90 g, 2.76 mmol) in tetrahydrofuran (25 mL) was added di-tert-butyl dicarbonate (0.76 mL, 3.31 mmol), and the mixture was stirred at room temperature for 12 hrs. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.16 g, yield 98%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.10-2.30 (1H, m), 2.39 (3H, s), 2.54 (3H, s), 2.78 (2H, d, J = 7.2 Hz), 3.50 (3H, s), 4.15 (2H, d, J = 4.9 Hz), 4.24 (1H, t, J = 4.9 Hz), 7.06 (2H, d, J = 7.9 Hz), 7.20 (2H, d, J = 7.9 Hz).

2) To a solution of methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.0 g, 2.34 mmol) in methanol (30 mL)

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was added 1N aqueous sodium hydroxide solution (10 mL), and the mixture was heated under reflux for 3 days. The reaction mixture was allowed to c l to room temperature, acidified with 0.5N hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was crystallized from water-methanol to give 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.58 g, yield 60%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:0.87 (6H, d, J = 6.4 Hz), 1.39 (9H, s), 1.95-2.10 (1H, m), 2.38 (3H, s), 2.67 (3H, s), 2.75 (2H, d, J = 7.2 Hz), 4.13 (2H, d, J = 4.7 Hz), 4.30 (1H, t, J = 4.7 Hz), 7.15 (2H, d, J = 7.9 Hz), 7.22 (2H, d, J = 7.9 Hz).

3) To a solution of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.20 g, 0.48 mmol) in 1,4-dioxane (4 mL) was added 4N hydrogen chloride 1,4-dioxane solution (4 mL, 16 mmol), and the mixture was stirred at room temperature for 2 hrs. The reaction mixture was concentrated under reduced pressure, and the obtained white solid was washed with diisopropyl ether to give 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid dihydrochloride(0.18 g, yield 95%) as a white powder.

^{1}H-NMR (DMSO-d_6) δ:0.98 (6H, d, J = 6.6 Hz), 2.05-2.30 (1H, m), 2.38 (3H, s), 2.65 (3H, s), 3.02 (2H, s), 3.83 (2H, d, J = 5.5 Hz), 7.26 (2H, d, J = 8.2 Hz), 7.32 (2H, d, J = 8.2 Hz), 8.45 (3H, brs).

Example 3

5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinamide dihydrochloride

1) A mixture of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.11 g, 0.27 mmol), 1-hydroxy-1H-benzotriazole ammonium salt (0.10 g, 0.65 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

hydrochloride (0.13 g, 0.65 mmol) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 2.5 days. The reaction mixture was partitioned between ethyl acetate (100 mL) and 0.1 M aqueous citric acid solution (50 mL). The organic layer and an extract obtained by extracting the aqueous layer with ethyl acetate were combined, and the mixture was washed successively with saturated aqueous sodium hydrogen carbonate and saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give tert-butyl {[5-(aminocarbonyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.090 g, yield 82%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.10-2.30 (1H, m), 2.39 (3H, s), 2.61 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 4.14 (2H, d, J = 4.7 Hz), 4.15-4.30 (1H, m), 5.22 (1H, brs), 5.41 (1H, brs), 7.11 (2H, d, J = 7.9 Hz), 7.23 (2H, d, J = 7.9 Hz).

2) 5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinamide dihydrochloride (0.050 g, yield 82%) was obtained as a white powder from tert-butyl {[5-(aminocarbonyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.065 g, 0.16 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.98 (6H, d, J = 6.6 Hz), 2.05-2.30 (1H, m), 2.37 (3H, s), 2.66 (3H, s), 3.02 (2H, s), 3.82 (2H, d, J = 4.9 Hz), 7.20-7.35 (4H, m), 7.54 (1H, brs), 7.84 (1H, brs), 8.32 (3H, brs).

Example 4

5-(aminomethyl)-N-(3-amino-3-oxopropyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinamide dihydrochloride

1) A mixture of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.12 g, 0.29 mmol), β-alaninamide hydrochloride (0.055 g, 0.44 mmol),

1-hydroxy-1H-benzotriazole (0.059 g, 0.44 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.084 g, 0.44 mmol), triethylamine (0.061 mL, 0.44 mmol) and N,N-dimethylformamide (5 mL) was stirred at room temperature for 14 hrs. The reaction mixture was partitioned between ethyl acetate-tetrahydrofuran (1:1, 100 mL) and 0.1 M aqueous citric acid solution (100 mL). The organic layer and an extract obtained by extracting the aqueous layer with ethyl acetate were combined, and the mixture was washed successively with saturated aqueous sodium hydrogen carbonate and saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give tert-butyl {[5-[(3-amino-3-oxopropyl)amino]carbonyl-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.075 g, yield 54%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.8 Hz), 1.38 (9H, s), 1.98 (2H, t, J = 6.0 Hz), 2.10-2.25 (1H, m), 2.38 (3H, s), 2.55 (3H, s), 2.76 (2H, d, J = 7.2 Hz), 3.36 (2H, q, J = 6.0 Hz), 4.11 (2H, d, J = 5.5 Hz), 4.23 (1H, brs), 5.23 (1H, brs), 5.38 (1H, brs), 6.22 (1H, t, J = 5.5 Hz), 7.09 (2H, d, J = 8.1 Hz), 7.19 (2H, d, J = 8.1 Hz).

2) 5-(Aminomethyl)-N-(3-amino-3-oxopropyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinamide dihydrochloride (0.048 g, 99%) was obtained as a white powder from tert-butyl {[5-[(3-amino-3-oxopropyl)amino]carbonyl-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.050 g, 0.10 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.97 (6H, d, J = 6.6 Hz), 1.98 (2H, t, J = 6.7 Hz), 2.10-2.25 (1H, m), 2.37 (3H, s), 2.57 (3H, s), 2.96 (2H, brs), 3.09 (2H, q, J = 6.7 Hz), 3.82 (2H, d, J = 5.3 Hz), 6.82 (1H, brs), 7.21 (2H, d, J = 8.0 Hz), 7.27 (2H, d, J = 8.0 Hz), 7.28 (1H, brs), 8.24 (3H, brs), 8.36 (1H, brs).

Example 5

[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetonitrile

1) A suspension of methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (3.4 g, 7.9 mmol) in toluene (80 mL) was cooled to -78°C, and 0.95 M diisobutylaluminum hydride toluene solution (33 mL, 32 mmol) was added dropwise thereto over 15 min. After stirring at -78°C for 1.5 hrs., the mixture was allowed to warm to 0°C, and further stirred for 30 min. Methanol (1 mL) and sodium sulfate 10 hydrate (10.2 g, 32 mmol) were added successively to the reaction mixture, and the mixture was stirred at room temperature for 1 hr. The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.9 g, yield 60%) as an oil.

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.32 (9H, s), 2.13-2.25 (1H, m), 2.42 (3H, s), 2.68 (3H, s), 2.75 (2H, d, J = 7.4 Hz), 4.05 (2H, d, J = 4.7 Hz), 4.19 (1H, brs), 4.36 (2H, d, J = 5.7 Hz), 7.05 (2H, d, J = 7.9 Hz), 7.24-7.26 (2H, m).

2) A mixture of tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.50 g, 1.3 mmol), triethylamine (0.35 mL, 2.5 mmol) and tetrahydrofuran (10 mL) was cooled to 0°C, and methanesulfonyl chloride (0.22 g, 1.9 mmol) was added dropwise thereto. After stirring at room temperature for 30 min, the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was dissolved in dimethyl sulfoxide (5 mL), and potassium cyanide (0.41 g, 6.3 mmol) was added thereto. The mixture was stirred at 60°C for 30 min. Ethyl acetate was added to the reaction mixture,

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and the mixture was washed successively with water and saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give tert-butyl {[5-(cyanomethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.36 g, yield 72%) as an oil.

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.8 Hz), 1.38 (9H, s), 2.16-2.25 (1H, m), 2.43 (3H, s), 2.66 (3H, s), 2.77 (2H, d, J = 7.2 Hz), 3.31 (2H, s), 4.07 (2H, d, J = 4.7 Hz), 7.04 (2H, d, J = 8.0 Hz), 7.31 (2H, d, J = 8.0 Hz).

3) Trifluoroacetic acid (5 mL) was added to tert-butyl {[5-(cyanomethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.11 g, 0.27 mmol), and the mixture was stirred at room temperature for 15 min. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate-tetrahydrofuran. The extract was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give [5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetonitrile (0.084 g, yield 99%) as an oil.

^{1}H-NMR ($CDCl_3$) δ:0.99 (6H, d, J = 6.6 Hz), 2.11-2.22 (1H, m), 2.45 (3H, s), 2.66 (3H, s), 2.80 (2H, d, J = 7.2 Hz), 3.47 (2H, s), 3.74 (2H, brs), 7.17 (2H, d, J = 7.8 Hz), 7.42 (2H, d, J = 7.8 Hz).

Example 6

2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetamide dihydrochloride

1) To a solution of tert-butyl {[5-(cyanomethyl)-2-isobutyl-6-methyl-4-(4-methylpheryl)pyridin-3-yl]methyl}carbamate (0.90 g, 2.2 mmol) in ethanol (20 mL) was added 2N aqueous sodium hydroxide solution (5.5 mL, 11 mmol), and the mixture was

heated under reflux for 2 hrs. 6N Hydrochloric acid was added to acidify the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give tert-butyl {[5-(2-amino-2-oxoethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.25 g, yield 27%) as a colorless solid.

2) Trifluoroacetic acid (5 mL) was added to tert-butyl {[5-(2-amino-2-oxoethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.25 g, 0.59 mmol), and the mixture was stirred at room temperature for 20 min. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate-tetrahydrofuran. The extract was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. 4N Hydrogen chloride 1,4-dioxane solution (4 mL, 16 mmol) was added to the residue, and the solvent was evaporated under reduced pressure. The residue was washed with diisopropyl ether to give 2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetamide dihydrochloride (0.19 g, yield 81%) as a white powder.

^{1}H-NMR (CD_3OD) δ:1.09-1.13 (6H, m), 2.09-2.22 (1H, m), 2.46 (3H, s), 2.77-2.80 (3H, m), 3.00-3.09 (2H, m), 3.51-3.55 (2H, m), 4.08 (2H, brs), 7.15-7.22 (2H, m), 7.47 (2H, d, J = 8.1 Hz).

Example 7

methyl [5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate dihydrochloride

1) To a solution of tert-butyl {[5-(cyanomethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.90 g, 2.2 mmol) in ethanol (20 mL) was added 2N aqueous sodium hydroxide solution (5.5 mL, 11 mmol), and the mixture was heated under reflux for 1.5 days. 6N Hydrochl ric acid was

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added to acidify the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was dissolved in N,N-dimethylformamide (5 mL). Methyl iodide (0.65 g, 4.4 mmol) and potassium carbonate (0.61 g, 4.4 mmol) were added thereto, and the mixture was stirred at room temperature for 1 hr. Ethyl acetate was added to the reaction mixture, and the mixture was washed successively with water and saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give methyl [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate (0.097 g, yield 10%) as an oil..

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.13-2.28 (1H, m), 2.40 (3H, s), 2.49 (3H, s), 2.75 (2H, d, J = 7.4 Hz), 3.36 (2H, s), 3.61 (3H, s), 4.04-4.05 (2H, m), 4.27 (1H, brs), 6.98 (2H, d, J = 7.8 Hz), 7.23 (2H, d, J = 7.8 Hz).

2) Methyl [5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate dihydrochloride (0.069 g, yield 76%) was obtained as a white powder from methyl [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate (0.097 g, 0.22 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (CD_3OD) δ:1.09-1.13 (6H, m), 2.12-2.26 (1H, m), 2.47 (3H, s), 2.84 (3H, s), 3.12 (2H, d, J = 7.4 Hz), 3.29-3.31 (2H, m), 3.63 (3H, s), 4.08 (2H, s), 7.19 (2H, d, J = 7.7 Hz), 7.48 (2H, d, J = 7.7 Hz).

Example 8

ethyl (2E)-3-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acrylate

1) To a solution of tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.95

g, 4.9 mmol) in tetrahydrofuran (50 mL) was added manganese dioxide (4.9 g, 56 mmol), and the mixture was stirred at room temperature for 19 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl {[5-formyl-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.25 g, yield 65%) as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.21-2.35 (1H, m), 2.43 (3H, s), 2.79 (3H, s), 2.82 (2H, d, J = 7.2 Hz), 4.15 (2H, d, J = 4.9 Hz), 4.38 (1H, brs), 7.10 (2H, d, J = 8.1 Hz), 7.29 (2H, d, J = 8.1 Hz), 9.71 (1H, s).

2) To a solution of triethyl phosphonoacetate (0.033 g, 1.5 mmol) in tetrahydrofuran (10 mL) was added sodium hydride (60% in oil, 0.060 g, 1.5 mmol) at 0°C, and the mixture was stirred f r 20 min. A solution of tert-butyl {[5-formyl-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.38 g, 0.98 mmol) in tetrahydrofuran (5 mL) was added to the reaction mixture, and the mixture was stirred at room temperature for 45 min. Ethyl acetate was added to the reaction mixture, and the mixture was washed successively with saturated brine, saturated aqueous ammonium chloride solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give ethyl (2E)-3-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acrylate (0.44 g, yield 96%) as an oil.

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.6 Hz), 1.23 (3H, t, J = 7.2 Hz), 1.39 (9H, s), 2.16-2.27 (1H, m), 2.40 (3H, s), 2.64 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 4.08-4.17 (4H, m), 4.21 (1H, brs), 5.76 (1H, d, J = 16.4 Hz), 6.95 (2H, d, J = 8.1 Hz), 7.23 (2H, d, J = 8.1 Hz), 7.37 (1H, d, J = 16.4 Hz).

3) A mixture of ethyl (2E)-3-[5-{[(tert-

butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acrylate (0.12 g, 0.25 mmol) and 4N hydrogen chloride 1,4-dioxane solution (5 mL, 20 mmol) was stirred at room temperature for 10 min. The solvent was evaporated under reduced pressure, and the residue was partitioned between ethyl acetate-tetrahydrofuran and saturated aqueous sodium hydrogen carbonate. The organic layer and an extract obtained by extracting the aqueous layer with ethyl acetate-tetrahydrofuran were combined, and the mixture was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give ethyl (2E)-3-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acrylate (0.059 g, yield 64%).

^{1}H-NMR ($CDCl_3$) δ:0.99 (6H, d, J = 6.6 Hz), 1.23 (3H, t, J = 7.2 Hz), 1.30 (2H, brs), 2.18-2.33 (1H, m), 2.40 (3H, s), 2.63 (3H, s), 2.79 (2H, d, J = 7.1 Hz), 3.60 (2H, s), 4.13 (2H, q, J = 7.2 Hz), 5.76 (1H, d, J = 16.4 Hz), 7.01 (2H, d, J = 8.0 Hz), 7.24 (2H, d, J = 8.0 Hz), 7.39 (1H, d, J = 16.4 Hz).

Example 9

(2E)-3-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acrylic acid dihydrochloride

1) To a solution of ethyl (2E)-3-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acrylate (0.32 g, 0.69 mmol) in tetrahydrofuran (10 mL) was added 1N aqueous sodium hydroxide solution (3.4 mL, 3.4 mmol), and the mixture was stirred at 60°C for 12 hrs. The reaction mixture was acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extracts were combined, and the mixture was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give (2E)-3-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-

2-methyl-4-(4-methylphenyl)pyridin-3-yl]acrylic acid (0.28 g, yield 93%) as a white solid.

^{1}H-NMR ($CDCl_3$) δ:0.96 (6H, d, J = 6.4 Hz), 1.39 (9H, s), 2.10-2.20 (1H, m), 2.39 (3H, s), 2.64 (3H, s), 2.79 (2H, d, J = 7.2 Hz), 4.00-4.20 (2H, m), 4.34 (1H, brs), 5.76 (1H, d, J = 16.4 Hz), 6.97 (2H, d, J = 7.5 Hz), 7.22 (2H, d, J = 7.5 Hz), 7.41 (1H, d, J = 16.4 Hz).

2) (2E)-3-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acrylic acid dihydrochloride (0.077 g, yield 90%) was obtained as a white powder from (2E)-3-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acrylic acid (0.093 g, 0.21 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (CD_3OD) δ:1.10 (6H, d, J = 6.6 Hz), 2.12-2.27 (1H, m), 2.46 (3H, brs), 2.84 (3H, s), 3.05 (2H, d, J = 7.5 Hz), 4.13 (2H, s), 5.98 (1H, d, J = 16.3 Hz), 7.20 (2H, d, J = 8.0 Hz), 7.25 (1H, d, J = 16.3 Hz), 7.46 (2H, d, J = 8.0 Hz).

Example 10

(2E)-3-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acrylamide dihydrochloride

1) tert-Butyl {[5-[(1E)-3-amino-3-oxoprop-1-en-1-yl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.19 g, yield 99%) was obtained from (2E)-3-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acrylic acid (0.19 g, 0.43 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR (CD_3OD) δ:0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.09-2.20 (1H, m), 2.37 (3H, s), 2.59 (3H, s), 2.74 (2H, d, J = 7.2 Hz), 3.99 (2H, s), 4.34 (1H, brs), 6.00 (1H, d, J = 16.2 Hz), 7.06 (2H, d, J = 8.1 Hz), 7.22-7.28 (3H, m).

2) (2E)-3-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acrylamide dihydrochloride (0.078 g, yield 99%) was obtained from tert-butyl {[5-[(1E)-3-amino-3-oxoprop-1-en-1-yl]-2-isobutyl-6-methyl-4-(4-

methylphenyl)pyridin-3-yl]methyl)carbamate (0.083 g, 0.19 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (CD_3OD) δ:1.11 (6H, d, J = 6.6 Hz), 2.13-2.22 (1H, m), 2.45 (3H, s), 2.87 (3H, s), 3.10 (2H, d, J = 7.5 Hz), 4.15 (2H, s), 6.12 (1H, d, J = 16.2 Hz), 7.11 (1H, d, J = 16.2 Hz), 7.23 (2H, d, J = 7.9 Hz), 7.45 (2H, d, J = 7.9 Hz).

Example 11

methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-phenylnicotinate

1) Methyl 5-cyano-6-isobutyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (10.7 g, yield 86%) was obtained as a white powder from 5-methyl-3-oxohexanenitrile (5.0 g, 40 mmol), benzaldehyde (4.2 g, 40 mmol) and methyl 3-aminocrotonate (4.6 g, 40 mmol) according to a method similar to the method of Example 1-2).

^{1}H-NMR ($CDCl_3$) δ:0.93 (3H, d, J = 6.6 Hz), 0.99 (3H, d, J = 6.6 Hz), 1.82-1.97 (1H, m), 2.18-2.34 (2H, m), 2.38 (3H, s), 3.57 (3H, s), 4.61 (1H, s), 5.69 (1H, brs), 7.18-7.32 (5H, m).

2) Methyl 5-cyano-6-isobutyl-2-methyl-4-phenylnicotinate (8.4 g, yield 80%) was obtained as a white powder from methyl 5-cyano-6-isobutyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (10.7 g, 34 mmol) according to a method similar to the method of Example 1-3).

^{1}H-NMR ($CDCl_3$) δ:1.01 (6H, d, J = 6.8 Hz), 2.21-2.35 (1H, m), 2.64 (3H, s), 2.96 (2H, d, J = 7.2 Hz), 3.57 (3H, s), 7.33-7.39 (2H, m), 7.44-7.50 (3H, m).

3) Methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-phenylnicotinate (0.21 g, yield 2.5%) was obtained as a white powder from methyl 5-cyano-6-isobutyl-2-methyl-4-phenylnicotinate (8.4 g, 27 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:1.02 (6H, d, J = 6.6 Hz), 2.17-2.33 (1H, m), 2.54 (3H, s), 2.81 (2H, d, J = 7.4 Hz), 3.46 (3H, s), 3.65 (2H, s), 7.20-7.25 (2H, m), 7.38-7.46 (3H, m).

Example 12

methyl 5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)-2-propylnicotinate

1) A mixture of methyl 3-oxohexanoate (7.2 g, 50 mmol), ammonium acetate (19.3 g, 250 mmol), acetic acid (3.0 g, 50 mmol) and toluene (500 mL) was heated under reflux using a Dean-Stark trap for 11 hrs. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and saturated brine. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give methyl 3-aminohex-2-enoate as a colorless oil.

Methyl 5-cyano-6-isobutyl-4-(4-methylphenyl)-2-propyl-1,4-dihydropyridine-3-carboxylate (11.8 g, yield 84%) was obtained as an oil from 5-methyl-3-oxohexanenitrile (5.0 g, 40 mmol), p-tolualdehyde (4.8 g, 40 mmol) and the aforementioned colorless oil of methyl 3-aminohex-2-enoate, according to a method similar to the method of Example 1-2).

^{1}H-NMR ($CDCl_3$) δ:0.93-1.05 (6H, m), 1.26 (3H, q, J = 7.2 Hz), 1.59-1.69 (2H, m), 1.83-1.96 (1H, m), 2.23-2.47 (2H, m), 2.30 (3H, s), 2.69-2.74 (2H, m), 3.57 (3H, s), 4.58 (1H, s), 5.65 (1H, brs), 7.09 (2H, d, J = 8.1 Hz), 7.13 (2H, d, J = 8.1 Hz).

2) Methyl 5-cyano-6-isobutyl-4-(4-methylphenyl)-2-propylnicotinate (9.4 g, yield 80%) was obtained as an oil from methyl 5-cyano-6-isobutyl-4-(4-methylphenyl)-2-propyl-1,4-dihydropyridine-3-carboxylate (11.8 g, 33 mmol) according to a method similar to the method of Example 1-3).

^{1}H-NMR ($CDCl_3$) δ:0.98 (3H, t, J = 7.4 Hz), 1.01 (6H, d, J = 6.6 Hz), 1.73-1.85 (2H, m), 2.22-2.35 (1H, m), 2.41 (3H, s), 2.78 (2H, m), 2.96 (2H, d, J = 7.4 Hz), 3.58 (3H, s), 7.23-7.32 (4H, m).

3) Methyl 5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)-2-propylnicotinate (0.78 g, yield 88%) was obtained as an oil from methyl 5-cyano-6-isobutyl-4-(4-methylphenyl)-2-propylnicotinate (0.88 g, 2.6 mmol) according to a method

similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.94-0.99 (9H, m), 1.70-1.83 (2H, m), 2.18-2.31 (1H, m), 2.39 (3H, s), 2.69-2.74 (2H, m), 2.81 (2H, d, J = 7.2 Hz), 3.48 (3H, s), 3.65 (2H, s), 7.12 (2H, d, J = 8.1 Hz), 7.21 (2H, d, J = 8.1 Hz).

Example 13

[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid dihydrochloride

1) To a solution of methyl [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate (0.25 g, 0.56 mmol) in tetrahydrofuran (15 mL) were added ethanol (10 mL) and 8N aqueous sodium hydroxide solution (3.0 mL, 24 mmol), and the mixture was heated under reflux for 3 hrs. The reaction mixture was acidified with 6N hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (0.16 g, yield 65%) as a white powder.

2) [5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid dihydrochloride (0.15 g, yield 99%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (0.16 g, 0.36 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (CD_3OD) δ:1.10 (6H, d, J = 6.4 Hz), 2.09-2.25 (1H, m), 2.48 (3H, s), 2.84 (3H, s), 3.10 (2H, d, J = 7.4 Hz), 3.60 (2H, s), 4.09 (2H, s), 7.20 (2H, d, J = 7.9 Hz), 7.49 (2H, d, J = 7.9 Hz).

Example 14

methyl 5-(aminomethyl)-6-isobutyl-2-(2-methoxy-2-oxoethyl)-4-

(4-methylphenyl)nicotinate

1) Dimethyl 3-aminopent-2-enedioate was obtained from dimethyl 1,3-acetonedicarboxylate (7.0 g, 40 mmol) according to a method similar to the method of Example 12-1).

Methyl 5-cyano-6-isobutyl-2-(2-methoxy-2-oxoethyl)-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (11.5 g, yield 75%) was obtained as a yellow oil from the obtained dimethyl 3-aminopent-2-enedioate, 5-methyl-3-oxohexanenitrile (5.0 g, 40 mmol) and p-tolualdehyde (4.8 g, 40 mmol).

^{1}H-NMR ($CDCl_3$) δ:0.94 (3H, d, J = 6.6 Hz), 0.98 (3H, d, J = 6.6 Hz), 1.85-2.00 (1H, m), 2.20-2.40 (2H, m), 2.31 (3H, s), 3.58 (3H, s), 3.77 (3H, s), 3.85-4.10 (2H, m), 4.59 (1H, s), 7.01 (1H, brs), 7.10 (2H, d, J = 8.1 Hz), 7.16 (2H, d, J = 8.1 Hz).

2) Methyl 5-cyano-6-isobutyl-2-(2-methoxy-2-oxoethyl)-4-(4-methylphenyl)nicotinate (3.2 g, yield 28%) was obtained as yellow-orange oil from methyl 5-cyano-6-isobutyl-2-(2-methoxy-2-oxoethyl)-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (11.5 g, 30 mmol) according to a method similar to the method of Example 1-3).

^{1}H-NMR ($CDCl_3$) δ:1.01 (6H, d, J = 6.6 Hz), 2.20-2.35 (1H, m), 2.41 (3H, s), 2.97 (2H, d, J = 7.2 Hz), 3.54 (3H, s), 3.71 (3H, s), 4.04 (2H, s), 7.20-7.30 (4H, m).

3) Methyl 5-(aminomethyl)-6-isobutyl-2-(2-methoxy-2-oxoethyl)-4-(4-methylphenyl)nicotinate (2.5 g, yield 77%) was obtained as a pale-yellow oil from methyl 5-cyano-6-isobutyl-2-(2-methoxy-2-oxoethyl)-4-(4-methylphenyl)nicotinate (3.2 g, 8.4 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.8 Hz), 1.39 (2H, brs), 2.15-2.35 (1H, m), 2.39 (3H, s), 2.82 (2H, d, J = 7.4 Hz), 3.45 (3H, s), 3.67 (2H, s), 3.70 (3H, s), 3.94 (2H, s), 7.05-7.25 (4H, m).

Example 15

methyl 5-(aminomethyl)-4-(2,6-difluorophenyl)-6-isobutyl-2-methylnicotinate

1) Methyl 5-cyano-4-(2,6-difluorophenyl)-6-isobutyl-2-methyl-1,4-dihydropyridine-3-carboxylate (14.8 g, yield 36%) was obtained as yellow crystals from 5-methyl-3-oxohexanenitrile (15.0 g, 120 mmol) and 2,6-difluorobenzaldehyde (17.0 g, 120 mmol) and methyl 3-aminocrotonate (13.8 g, 120 mmol) according to a method similar to the method of Example 1-2).

^{1}H-NMR ($CDCl_3$) δ:0.95-1.05 (6H, m), 1.80-2.05 (1H, m), 2.10-2.45 (2H, m), 2.31 (3H, s), 3.56 (3H, s), 5.21 (1H, s), 5.87 (1H, brs), 6.75-6.90 (2H, m), 7.05-7.25 (1H, m).

2) Methyl 5-cyano-4-(2,6-difluorophenyl)-6-isobutyl-2-methylnicotinate (11.7 g, yield 80%) was obtained as yellow crystals from methyl 5-cyano-4-(2,6-difluorophenyl)-6-isobutyl-2-methyl-1,4-dihydropyridine-3-carboxylate (14.8 g, 43 mmol) according to a method similar to the method of Example 1-3).

^{1}H-NMR ($CDCl_3$) δ:1.15 (6H, d, J = 6.6 Hz), 2.15-2.40 (1H, m), 2.72 (3H, s), 2.97 (2H, d, J = 7.0 Hz), 3.65 (3H, s), 6.95-7.10 (2H, m), 7.35-7.55 (1H, m).

3) Methyl 5-(aminomethyl)-4-(2,6-difluorophenyl)-6-isobutyl-2-methylnicotinate (9.8 g, yield 83%) was obtained as pale-yellow solid from methyl 5-cyano-4-(2,6-difluorophenyl)-6-isobutyl-2-methylnicotinate (11.7 g, 34 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.99 (6H, d, J = 6.6 Hz), 1.51 (2H, brs), 2.15-2.35 (1H, m), 2.60 (3H, s), 2.83 (2H, d, J = 7.5 Hz), 3.56 (3H, s), 3.62 (2H, s), 6.95-7.05 (2H, m), 7.35-7.50 (1H, m).

melting point: 48-49°C

Example 16

methyl 5-(aminomethyl)-4-(4-fluorophenyl)-6-isobutyl-2-methylnicotinate

1) Methyl 5-cyano-4-(4-fluorophenyl)-6-isobutyl-2-methyl-1,4-dihydropyridine-3-carboxylate (27.4 g, yield 70%) was obtained as a yellow oil from 5-methyl-3-oxohexanenitrile (15.0 g, 120 mmol), 4-fluorobenzaldehyde (14.9 g, 120 mmol) and methyl 3-aminocrotonate (13.8 g, 120 mmol) according to a method similar

to the method of Example 1-2).

2) Methyl 5-cyano-4-(4-fluorophenyl)-6-isobutyl-2-methylnicotinate (24.0 g, yield 61%) was obtained as a yellow oil from methyl 5-cyano-4-(4-fluorophenyl)-6-isobutyl-2-methyl-1,4-dihydropyridine-3-carboxylate (27 g, 82 mmol) according to a method similar to the method of Example 1-3).

^{1}H-NMR ($CDCl_3$) δ:1.01 (6H, d, J = 6.6 Hz), 2.15-2.40 (1H, m), 2.64 (3H, s), 2.96 (2H, d, J = 7.2 Hz), 3.61 (3H, s), 7.10-7.40 (4H, m).

3) Methyl 5-(aminomethyl)-4-(4-fluorophenyl)-6-isobutyl-2-methylnicotinate (11.2 g, yield 85%) was obtained as a pale yellow solid from methyl 5-cyano-4-(4-fluorophenyl)-6-isobutyl-2-methylnicotinate (13.0 g, 40 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.6 Hz), 1.26 (2H, brs), 2.15-2.35 (1H, m), 2.54 (3H, s), 2.81 (2H, d, J = 7.2 Hz), 3.51 (3H, s), 3.65 (2H, s), 7.00-7.30 (4H, m).

melting point: 55-57°C

Example 17

5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)-2-propylnicotinic acid dihydrochloride

1) Methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)-2-propylnicotinate (0.71 g, yield 71%) was obtained as a white solid from methyl 5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)-2-propylnicotinate (0.78 g, 2.2 mmol) according to a method similar to the method of Example 2-1).

^{1}H-NMR ($CDCl_3$) δ:0.94-0.99 (9H, m), 1.39 (9H, s), 1.70-1.83 (2H, m), 2.16-2.27 (1H, m), 2.38 (3H, s), 2.70-2.75 (2H, m), 2.79 (2H, d, J = 7.2 Hz), 3.48 (3H, s), 4.14 (2H, d, J = 4.9 Hz), 4.24 (1H, brs), 7.06 (2H, d, J = 7.9 Hz), 7.20 (2H, d, J = 7.9 Hz).

2) 5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)-2-propylnicotinic acid (0.59 g, yield 86%) was

obtained from methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)-2-propylnicotinate (0.71 g, 1.6 mmol) according to a method similar to the method of Example 2-2).

^{1}H-NMR ($CDCl_3$) δ:0.94-1.05 (9H, m), 1.39 (9H, s), 1.72-1.84 (2H, m), 2.12-2.22 (1H, m), 2.38 (3H, s), 2.81-2.92 (4H, m), 4.40-4.09 (2H, m), 7.20 (2H, d, J = 8.3 Hz), 7.26 (2H, d, J = 8.3 Hz).

3) 5-(Aminomethyl)-6-isobutyl-4-(4-methylphenyl)-2-propylnicotinic acid dihydrochloride (0.50 g, yield 90%) was obtained as a white powder from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)-2-propylnicotinic acid (0.59 g, 1.3 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (CD_3OD) δ:1.04-1.13 (9H, m), 1.76-1.91 (2H, m), 2.13-2.25 (1H, m), 2.44 (3H, s), 3.01-3.18 (4H, m), 4.20 (2H, brs), 7.28-7.36 (2H, m), 7.43 (2H, d, J = 7.9 Hz).

Example 18

5-(aminomethyl)-6-isobutyl-2-methyl-4-phenylnicotinic acid dihydrochloride

1) Methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-phenylnicotinate (9.4 g, yield 83%) was obtained as a white solid from methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-phenylnicotinate (8.5 g, 27 mmol) according to a method similar to the method of Example 2-1).

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.15-2.20 (1H, m), 2.55 (3H, s), 2.79 (2H, d, J = 7.2 Hz), 3.46 (3H, s), 4.14 (2H, d, J = 4.9 Hz), 4.24 (1H, brs), 7.14-7.21 (2H, m), 7.37-7.44 (3H, m).

2) 5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-phenylnicotinic acid (0.39 g, yield 40%) was obtained as a white solid from methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-phenylnicotinate (1.0 g, 2.4 mmol) according to a method similar to the method of Example 2-2).

3) 5-(Aminomethyl)-6-isobutyl-2-methyl-4-phenylnicotinic acid dihydrochloride (0.25 g, yield 86%) was obtained as a white powder from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-phenylnicotinic acid (0.39 g, 0.98 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (CD_3OD) δ:1.04-1.15 (6H, m), 2.12-2.28 (1H, m), 2.78-2.89 (3H, m), 3.01-3.14 (2H, m), 4.13-4.20 (2H, m), 7.38-7.47 (2H, m), 7.56-7.63 (3H, m).

Example 19

methyl 5-[(dimethylamino)methyl]-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate

A mixture of methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.50 g, 1.6 mmol), formic acid (5 mL) and formalin (5 mL) was stirred at 100°C for 12 hrs. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 5-[(dimethylamino)methyl]-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.10 g, yield 19%).

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.8 Hz), 1.97 (6H, s), 2.14-2.28 (1H, m), 2.39 (3H, s), 2.53 (3H, s), 2.89 (2H, d, J = 7.4 Hz), 3.23 (2H, s), 3.48 (3H, s), 7.04 (2H, d, J = 8.0 Hz), 7.17 (2H, d, J = 8.0 Hz).

Example 20

methyl 5-(aminomethyl)-2-methyl-6-isobutyl-[4,4'-bipyridine]-3-carboxylate

1) Methyl 5-cyano-6-isobutyl-2-methyl-1,4-dihydro-4,4'-bipyridine-3-carboxylate (26.4 g, yield 71%) was obtained as a yellow oil from 5-methyl-3-oxohexanenitrile (15.0 g, 120 mmol), isonicotinaldehyde (12.8 g, 120 mmol) and methyl 3-aminocrotonate (13.8 g, 120 mmol) according to a method similar to the method of Example 1-2).

2) T a solution of methyl 5-cyano-6-isobutyl-2-methyl-1,4-dihydro-4,4'-bipyridine-3-carboxylate (20 g, 64 mmol) in acetone (150 mL) was added diammonium cerium nitrate (45 g, 82 mmol), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was cooled to 0°C and partitioned between ethyl acetate and 2N sodium hydroxide. The organic layer and an extract obtained by extracting the aqueous layer with ethyl acetate were combined and the mixture was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give methyl 5-cyano-6-isobutyl-2-methyl-4,4'-bipyridine-3-carboxylate (10.2 g, yield 51%) as a yellow oil.

3) Methyl 5-(aminomethyl)-2-methyl-6-isobutyl-[4,4'-bipyridine]-3-carboxylate (10.9 g, yield 72%) was obtained as pale-yellow solid from methyl 5-cyano-6-isobutyl-2-methyl-4,4'-bipyridine-3-carboxylate (15.0 g, 48 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.99 (6H, d, J = 6.6 Hz), 1.33 (2H, brs), 2.15-2.40 (1H, m), 2.57 (3H, s), 2.82 (2H, d, J = 7.2 Hz), 3.49 (3H, s), 3.61 (2H, s), 7.15-7.25 (2H, m), 8.65-8.70 (2H, m).

melting point: 63-65°C

Example 21

methyl 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate

1) 5,5-Dimethyl-3-oxohexanenitrile (92.0 g, yield 99%) was obtained as an oil from methyl 3,3-dimethylbutanoate (86.0 g, 0.66 mol) according to a method similar to the method of Example 1-1).

^{1}H-NMR ($CDCl_3$) δ:1.05 (9H, s), 2.49 (2H, s), 3.43 (2H, s).

2) A mixture of 5,5-dimethyl-3-oxohexanenitrile (22.0 g, 158 mmol), p-tolualdehyde (19 g, 158 mmol), piperidine (1.3 g, 15.8 mmol), acetic acid (1.9 g, 31.6 mmol) and toluene (300 mL) was heated under reflux for 12 hrs. using a Dean-Stark trap. After

allowing to cool to room temperature, the reaction mixture was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in methanol (50 mL). Methyl 3-aminocrotonate (18.2 g, 158 mmol) was added thereto and the mixture was heated under reflux for 6 hrs. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give methyl 5-cyano-2-methyl-4-(4-methylphenyl)-6-neopentyl-1,4-dihydropyridine-3-carboxylate (23 g, yield 43%) as an oil.

^{1}H-NMR ($CDCl_3$) δ:1.01 (9H, s), 0.98 (3H, d, J = 6.6 Hz), 1.80-2.00 (1H, m), 2.14-2.41 (2H, m), 2.31 (3H, s), 2.37 (3H, s), 3.58 (3H, s), 4.57 (1H, s), 5.56 (1H, brs), 7.06-7.16 (4H, m).

3) Methyl 5-cyano-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate (12 g, yield 60%) was obtained as colorless crystals from methyl 5-cyano-2-methyl-4-(4-methylphenyl)-6-neopentyl-1,4-dihydropyridine-3-carboxylate (20 g, 59.4 mmol) according to a method similar to the method of Example 1-3).

^{1}H-NMR ($CDCl_3$) δ:1.06 (9H, s), 2.41 (3H, s), 2.63 (3H, s), 3.01 (2H, s), 3.61 (3H, s), 7.26 (4H, m).

melting point: 139-140°C

4) Methyl 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate (2.3 g, yield 56%) was obtained as colorless crystals from methyl 5-cyano-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate (4 g, 11.9 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:1.02 (9H, s), 1.44 (2H, brs), 2.39 (3H, s), 2.53 (3H, s), 2.88 (2H, s), 3.50 (3H, s), 3.72 (2H, s), 7.12 (2H, m), 7.21 (2H, m).

melting point: 119-120°C

Example 22

5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid dihydrochloride

1) To a solution f methyl 5-(aminomethyl)-2-methyl-4-(4-

methylphenyl)-6-neopentylnicotinate (1.0 g, 2.9 mmol) in tetrahydrofuran (25 mL) was added di-tert-butyl dicarbonate (0.65 g, 3.0 mmol), and the mixture was stirred at room temperature for 1 hr. 8N Aqueous sodium hydroxide solution (2 mL) and methanol (10 mL) were added to the reaction mixture, and the mixture was heated under reflux for 3 days. The reaction mixture was allowed to cool to room temperature, acidified with 1N hydrochloric acid, and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was crystallized from diisopropyl ether to give 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid (0.5 g, yield 42%) as crystals.

^{1}H-NMR ($CDCl_3$) δ:0.88 (9H, s), 1.36 (9H, s), 2.38 (3H, s), 2.72 (3H, s), 2.88 (2H, s), 4.21 (2H, brs), 4.29 (1H, brs), 7.18 (2H, d, J = 8.3 Hz), 7.23 (2H, d, J = 8.3 Hz).

melting point: 216-217°C

2) 4N Hydrogen chloride 1,4-dioxane solution (5 mL) was added to 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid (0.30 g, 0.7 mmol), and the mixture was stirred at room temperature for 17 hr. The reaction mixture was concentrated under reduced pressure and the obtained white solid was washed with diethyl ether to give 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid dihydrochloride (0.2 g, yield 71%) as a white powder.

^{1}H-NMR (DMSO-d_6) δ:1.02 (9H, s), 2.37 (3H, s), 2.59 (3H, s), 3.04 (2H, s), 3.86 (2H, d, J = 5.5 Hz), 7.23 (2H, d, J = 8.1 Hz), 7.30 (2H, d, J = 8.1 Hz), 8.24 (3H, brs).

Example 23

tert-butyl 5-(aminomethyl)-4-(4-chlorophenyl)-6-isobutyl-2-methylnicotinate

1) A mixture of tert-butyl acetoacetate (580 mL, 3.5 mol), 25%

aqueous ammonia (1200 mL) and methanol (1000 mL) was stirred at room temperature for 14 hrs. After concentrating under reduced pressure, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give tert-butyl 3-aminocrotonate (550 g, yield 99%) as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ:1.47 (9H, s), 1.87 (3H, s), 4.46 (1H, s).

2) tert-Butyl 4-(4-chlorophenyl)-5-cyano-6-isobutyl-2-methyl-1,4-dihydropyridine-3-carboxylate (7.6 g, yield 62%) was obtained as a white powder from 5-methyl-3-oxohexanenitrile (4.0 g, 32 mmol), 4-chlorobenzaldehyde (4.5 g, 32 mmol) and tert-butyl 3-aminocrotonate (5.0 g, 32 mmol) according to a method similar to the method of Example 1-2).

^{1}H-NMR ($CDCl_3$) δ:0.93 (3H, d, J = 6.6 Hz), 0.99 (3H, d, J = 6.6 Hz), 1.29 (9H, s), 1.80-1.95 (1H, m), 2.10-2.30 (2H, m), 2.34 (3H, s), 4.54 (1H, s), 5.56 (1H, brs), 7.10-7.20 (2H, m), 7.25-7.30 (2H, m).

melting point: 185-186°C

3) To a solution of tert-butyl 4-(4-chlorophenyl)-5-cyano-6-isobutyl-2-methyl-1,4-dihydropyridine-3-carboxylate (7.6 g, 20 mmol) in acetone (200 mL) was added an aqueous solution (40 mL) of diammonium cerium nitrate (27 g, 49 mmol) at room temperature over 5 min. The reaction mixture was partitioned between ethyl acetate and water. The organic layer and an extract obtained by extracting the aqueous layer with ethyl acetate were combined, and the mixture was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give tert-butyl 4-(4-chlorophenyl)-5-cyano-6-isobutyl-2-methylnicotinate (7.2 g, yield 95%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:1.01 (6H, d, J = 6.8 Hz), 1.27 (9H, s), 2.15-2.35 (1H, m), 2.65 (3H, s), 2.94 (2H, d, J = 7.2 Hz), 7.30-7.35

(2H, m), 7.40-7.50 (2H, m).

melting point: 70-72°C

4) A mixture of tert-butyl 4-(4-chlorophenyl)-5-cyano-6-isobutyl-2-methylnicotinate (1.0 g, 2.6 mmol), Raney-cobalt (4 mL), 25% aqueous ammonia (2 mL), tetrahydrofuran (20 mL) and methanol (40 mL) was stirred in a sealed tube under 0.5 MPa hydrogen atmosphere at room temperature for 5 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 10% aqueous potassium carbonate solution. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give tert-butyl 5-(aminomethyl)-4-(4-chlorophenyl)-6-isobutyl-2-methylnicotinate (0.98 g, yield 97%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.8 Hz), 1.22 (9H, s), 1.42 (2H, brs), 2.15-2.30 (1H, m), 2.55 (3H, s), 2.79 (2H, d, J = 7.2 Hz), 3.61 (2H, s), 7.21 (2H, d, J = 8.3 Hz), 7.41 (2H, d, J = 8.3 Hz).

melting point: 81-83°C

Example 24

5-(aminomethyl)-4-(4-chlorophenyl)-6-isobutyl-2-methylnicotinic acid hydrochloride

1) A mixture of tert-butyl 5-(aminomethyl)-4-(4-chlorophenyl)-6-isobutyl-2-methylnicotinate (0.60 g, 1.5 mmol) and trifluoroacetic acid (4 mL) was stirred at 50°C for 4 hrs. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in 1,4-dioxane (4 mL). 4N Hydrogen chloride 1,4-dioxane solution (4 mL, 16 mmol) was added to the obtained solution, and the mixture was concentrated under reduced pressure. The residue was washed with diisopropyl ether to give 5-(aminomethyl)-4-(4-chlorophenyl)-6-isobutyl-2-methylnicotinic acid dihydrochloride (0.63 g, yield 99%) as a

colorless oil.

2) 5-(Aminomethyl)-4-(4-chlorophenyl)-6-isobutyl-2-methylnicotinic acid dihydrochloride (0.63 g, 1.5 mmol) was dissolved in isopropanol (10 mL), and propylene oxide (0.27 g, 4.6 mmol) was added thereto. The mixture was stirred at room temperature for 3 hrs. The reaction mixture was concentrated under reduced pressure, and the obtained oil was crystallized from isopropanol-diisopropyl ether to give 5-(aminomethyl)-4-(4-chlorophenyl)-6-isobutyl-2-methylnicotinic acid hydrochloride (0.43 g, 76%) as a white powder.

^{1}H-NMR (DMSO-d_6) δ:0.96 (6H, d, J = 6.6 Hz), 2.15-2.30 (1H, m), 2.49 (3H, s), 2.78 (2H, d, J = 7.2 Hz), 3.75 (2H, s), 7.34 (2H, d, J = 7.5 Hz), 7.54 (2H, d, J = 7.5 Hz), 8.43 (1H, brs).

Example 25

tert-butyl 5-(aminomethyl)-6-isobutyl-2-isopropyl-4-(4-methylphenyl)nicotinate

1) To a solution of Meldrum's acid (14.41 g, 0.1 mol) and pyridine (16.2 mL, 0.2 mol) in dichloromethane (100 mL) was added dropwise isobutyryl chloride (13.4 mL, 0.11 mol) at 0°C over 30 min., and the mixture was stirred at 0°C for 2 hrs. The reaction mixture was poured into 0.5N hydrochloric acid, and the mixture was extracted with dichloromethane. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. A mixture of the obtained residue, tert-butanol (11.2 g, 150 mmol) and toluene (100 mL) was heated under reflux for 6 hrs. After allowing to cool to room temperature, the reaction mixture was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give tert-butyl 4-methyl-3-oxopentanoate as a crude product (9.31 g). A mixture of the crude product (9.31 g), 25% aqueous ammonia (100 mL) and methanol (100 mL) was stirred at room temperature for 12 hrs. The reaction mixture was concentrated under reduced pressure,

and partitioned between ethyl acetate and water. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give tert-butyl 3-amino-4-methylpent-2-enoate as a crude product (9.26 g).

2) tert-Butyl 5-cyano-6-isobutyl-2-isopropyl-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (12.11 g, yield 76%) was obtained as colorless crystals from 5-methyl-3-oxohexanenitrile (5.0 g, 40 mmol), p-tolualdehyde (4.8 g, 40 mmol) and the crude product (9.26 g) of tert-butyl 3-amino-4-methylpent-2-enoate obtained in the aforementioned 1), according to a method similar to the method of Example 1-2).

3) tert-Butyl 5-cyano-6-isobutyl-2-isopropyl-4-(4-methylphenyl)nicotinate (2.88 g, yield 73%) was obtained as an oil from tert-butyl 5-cyano-6-isobutyl-2-isopropyl-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (3.94 g, 10 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:1.01 (6H, d, J = 6.6 Hz), 1.25 (9H, s), 1.32 (6H, d, J = 6.6 Hz), 2.26-2.35 (1H, m), 2.40 (3H, s), 2.94 (2H, d, J = 7.2 Hz), 3.14-3.23 (1H, m), 7.26-7.35 (4H, m).

4) tert-Butyl 5-(aminomethyl)-6-isobutyl-2-isopropyl-4-(4-methylphenyl)nicotinate (2.15 g, yield 77%) was obtained as a white powder from tert-butyl 5-cyano-6-isobutyl-2-isopropyl-4-(4-methylphenyl)nicotinate (2.74 g, 7 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.99 (6H, d, J = 6.6 Hz), 1.18 (9H, s), 1.30 (6H, d, J = 6.6 Hz), 1.39 (2H, brs), 2.26-2.35 (1H, m), 2.39 (3H, s), 2.78 (2H, d, J = 6.9 Hz), 3.04-3.14 (1H, m), 3.60 (2H, s), 7.13 (2H, d, J = 8.2 Hz), 7.20 (2H, d, J = 8.2 Hz).

Example 26

5-(aminomethyl)-6-isobutyl-2-isopropyl-4-(4-methylphenyl)nicotinic acid dihydrochloride

5-(Aminomethyl)-6-isobutyl-2-isopropyl-4-(4-

methylphenyl)nicotinic acid dihydrochloride (0.37 g, yield 90%) was obtained as a white powder from tert-butyl 5-(aminomethyl)-6-isobutyl-2-isopropyl-4-(4-methylphenyl)nicotinate (0.40 g, 1 mmol) according to a method similar to the method of Example 24-1).

^{1}H-NMR (DMSO-d_6) δ:0.99 (6H, d, J = 6.6 Hz), 1.03 (6H, d, J = 6.6 Hz), 2.23-2.37 (4H, m), 2.85 (2H, d, J = 6.9 Hz), 3.04-3.13 (1H, m), 3.77 (2H, d, J = 5.4 Hz), 7.22 (2H, d, J = 8.1 Hz), 7.28 (2H, d, J = 8.1 Hz), 8.21 (3H, brs).

Example 27

tert-butyl 5-(aminomethyl)-4-(4-chlorophenyl)-2-methyl-6-neopentylnicotinate

1) tert-Butyl 4-(4-chlorophenyl)-5-cyano-2-methyl-6-neopentyl-1,4-dihydropyridine-3-carboxylate (2.5 g, yield 38%) was obtained as a white powder from 5,5-dimethyl-3-oxohexanenitrile (2.6 g, 18.0 mmol), 4-chlorobenzaldehyde (2.3 g, 16.0 mmol) and tert-butyl 3-aminocrotonate (2.5 g, 16.0 mmol) according to a method similar to the method of Example 1-2).

^{1}H-NMR ($CDCl_3$) δ:1.01 (9H, s), 1.29 (9H, s), 2.17 (1H, d, J = 13.9 Hz), 2.34 (3H, s), 2.35 (1H, d, J = 13.9 Hz), 4.55 (1H, s), 5.46 (1H, brs), 7.10-7.35 (4H, m).

melting point: 208-210°C

2) tert-Butyl 4-(4-chlorophenyl)-5-cyano-2-methyl-6-neopentylnicotinate (2.1 g, yield 90%) was obtained as a pale-yellow powder from tert-butyl 4-(4-chlorophenyl)-5-cyano-2-methyl-6-neopentyl-1,4-dihydropyridine-3-carboxylate (2.4 g, 5.9 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:1.06 (9H, s), 1.28 (9H, s), 2.65 (3H, s), 3.00 (2H, s), 7.30-7.35 (2H, m), 7.45-7.50 (2H, m).

melting point: 94-95°C

3) tert-Butyl 5-(aminomethyl)-4-(4-chlorophenyl)-2-methyl-6-neopentylnicotinate (0.93 g, yield 92%) was obtained as a white powder from tert-butyl 4-(4-chlorophenyl)-5-cyano-2-methyl-6-

neopentylnicotinate (1.0 g, 2.5 mmol) according to a meth d similar to the method of Example 23-4).

^{1}H-NMR ($CDCl_3$) δ:1.02 (9H, s), 1.22 (9H, s), 1.43(2H, brs), 2.55 (3H, s), 2.86 (2H, s), 3.66 (2H, s), 7.15-7.25 (2H, m), 7.35-7.45 (2H, m).

melting point: 116-118°C

Example 28

5-(aminomethyl)-4-(4-chlorophenyl)-2-methyl-6-neopentylnicotinic acid dihydrochloride

5-(Aminomethyl)-4-(4-chlorophenyl)-2-methyl-6-neopentylnicotinic acid dihydrochloride (1.0 g, yield 98%) was obtained as a white powder from tert-butyl 5-(aminomethyl)-4-(4-chlorophenyl)-2-methyl-6-neopentylnicotinate (0.95 g, 2.4 mmol) according to a method similar to the method of Example 24-1).

^{1}H-NMR (DMSO-d_6) δ:1.02 (9H, s), 2.56 (3H, s), 2.94 (2H, s), 3.84 (2H, d, J = 5.5 Hz), 7.35-7.40 (2H, m), 7.55-7.60 (2H, m), 8.20 (3H, brs).

melting point: 246-248°C

Example 29

tert-butyl 5-(aminomethyl)-4-(4-chlorophenyl)-2,6-dineopentylnicotinate

1) To a solution (30 mL) of piperidine (0.94 g, 11 mmol) and acetic acid (0.66 g, 11 mmol) in isopropanol was added dropwise a solution (300 mL) of 5,5-dimethyl-3-oxohexanenitrile (17.0 g, 110 mmol) and p-chlorobenzaldehyde (15.5 g, 110 mmol) in isopropanol at room temperature over 30 min. and the mixture was stirred for 3 days. The solvent was evaporated under reduced pressure, and the residue was partitioned between ethyl acetate and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to give 3-(4-chlorophenyl)-2-(3,3-dimethylbutanoyl)acrylonitrile as a crude product (35.2 g).

2) tert-Butyl 3-amino-5,5-dimethylhex-2-enoate was obtained as

a crude product (13 g) from Meldrum's acid (8.65 g, 60 mmol) and tert-butylacetyl chloride (9.2 mL, 66 mmol) according to a method similar to the method of Example 25-1).

3) tert-Butyl 4-(4-chlorophenyl)-5-cyano-2,6-dineopentyl-1,4-dihydropyridine-3-carboxylate (2.03 g, yield 15%) was obtained as a yellow oil from the crude product (11.7 g) obtained in the aforementioned 1), and the crude product (13.0 g) obtained in the aforementioned 2), according to a method similar to the method of Example 1-2). That is, the aforementioned two kinds of crude products were dissolved in methanol (40 mL) and the mixture was heated under reflux for 3.5 hrs. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give tert-butyl 4-(4-chlorophenyl)-5-cyano-2,6-dineopentyl-1,4-dihydropyridine-3-carboxylate.

^{1}H-NMR ($CDCl_3$) δ:1.00 (9H, s), 1.03 (9H, s), 1.29 (9H, s), 2.24 (4H, s), 4.58 (1H, brs), 5.37 (1H, brs), 7.20-7.32 (4H, m).

4) tert-Butyl 4-(4-chlorophenyl)-5-cyano-2,6-dineopentylnicotinate (0.75 g, yield 38%) was obtained from tert-butyl 4-(4-chlorophenyl)-5-cyano-2,6-dineopentyl-1,4-dihydropyridine-3-carboxylate (2.03 g, 4.44 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:1.04 (9H, s), 1.07 (9H, s), 1.24 (9H, s), 2.84 (2H, s), 3.00 (2H, s), 7.31 (2H, d, J = 8.67 Hz), 7.45 (2H, d, J = 8.67 Hz).

5) tert-Butyl 5-(aminomethyl)-4-(4-chlorophenyl)-2,6-dineopentylnicotinate (0.35 g, yield 46%) was obtained as a pale-yellow solid from tert-butyl 4-(4-chlorophenyl)-5-cyano-2,6-dineopentylnicotinate (0.75 g, 1.65 mmol) according to a method similar to the method of Example 23-4).

^{1}H-NMR ($CDCl_3$) δ:1.02 (9H, s), 1.04 (9H, s), 1.18 (9H, s), 2.74 (2H, s), 2.86 (2H, s), 3.64 (2H, s), 7.21 (2H, d, J = 8.48 Hz), 7.40 (2H, d, J = 8.48 Hz).

Example 30

5-(aminomethyl)-4-(4-chlorophenyl)-2,6-dineopentylnicotinic acid dihydrochl ride

5-(Aminomethyl)-4-(4-chlorophenyl)-2,6-dineopentylnicotinic acid dihydrochloride (0.21 g, yield 69%) was obtained as a white solid from tert-butyl 5-(aminomethyl)-4-(4-chlorophenyl)-2,6-dineopentylnicotinate (0.30 g, 0.653 mmol) according to a method similar to the method of Example 24-1).

^{1}H-NMR ($CDCl_3$) δ:0.99 (9H, s), 1.03 (9H, s), 2.77 (2H, s), 2.91 (2H, s), 3.83 (2H, d, J = 5.65 Hz), 7.35 (2H, d, J = 8.48 Hz), 7.54 (2H, d, J = 8.29 Hz), 8.12 (2H, brs).

Example 31

5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid hemifumarate (to be sometimes referred to as bis[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid] fumarate in this specification)

1) To a mixture of 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid dihydrochloride (5.99 g, 15.0 mmol), tetrahydrofuran (50 mL) and 1 M aqueous sodium hydroxide solution (50 mL) was added dropwise benzyl chloroformate (95%, 2.48 mL, 16.5 mmol) at room temperature. The obtained mixture was stirred for 2 hrs., and 0.1 M hydrochloric acid (100 mL) was added. The mixture was extracted with ethyl acetate-tetrahydrofuran (1:1). The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran to give 5-({[(benzyloxy)carbonyl]amino}methyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid (5.57 g, 81%) as colorless powder crystals.

^{1}H-NMR (DMSO-d_6) δ:0.98 (9H, s), 2.33 (3H, s), 2.44 (3H, s), 2.70 (2H, s), 3.97 (2H, d, J = 4.1 Hz), 4.98 (2H, s), 7.15-7.20 (4H, m), 7.27-7.42 (6H, m), 12.96 (1H, brs).

2) A mixture of 5-({[(benzyloxy)carbonyl]amino}methyl)-2-

methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid (5.5 g, 12 mmol), 5% palladium-carbon (11.0 g), tetrahydrofuran (100 mL) and ethanol (100 mL) was stirred overnight under a hydrogen atmosphere at room temperature. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was recrystallized from methanol to give 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid (2.46 g, 63%) as colorless powder crystals.

^{1}H-NMR (DMSO-d_6) δ:0.96 (9H, s), 2.33 (3H, s), 2.36 (3H, s), 2.76 (2H, s), 3.56 (2H, s), 7.12-7.18 (4H, m).

3) 5-(Aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid (1.14 g, 3.50 mmol) and fumaric acid (0.203 g, 1.75 mmol) were dissolved in water (150 mL) with heating. The obtained aqueous solution was concentrated under reduced pressure. The residue was washed with ethanol and recrystallized from water to give 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid hemifumarate (0.902 g, 67%) as colorless powder crystals.

^{1}H-NMR (DMSO-d_6) δ:0.97 (9H, s), 2.34 (3H, s), 2.40 (3H, s), 2.77 (2H, s), 3.65 (2H, s), 6.45 (1H, s), 7.14-7.21 (4H, m).

Example 32

tert-butyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate

1) tert-Butyl 5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (159 g, yield 27%) was obtained as a white solid from tert-butyl 3-aminocrotonate (253 g, 1.60 mol) according to a method similar to the method of Example 1-2). Subsequently, tert-butyl 5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (40.8 g, yield 99%) was obtained as a yellow solid from tert-butyl 5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (41.0 g, 112 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:1.01 (6H, d, J = 6.9 Hz), 1.26 (9H, s), 2.21-2.32 (1H, m), 2.41 (3H, s), 2.64 (3H, s), 2.93 (2H, d, J = 7.5 Hz), 7.18-7.32 (4H, m).

2) tert-Butyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (502 g, yield 96%) was obtained as a white solid from tert-butyl 5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (515 g, 1.42 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.6 Hz), 1.19 (9H, s), 2.13-2.31 (1H, m), 2.39 (3H, s), 2.56 (3H, s), 2.79 (2H. d, J = 7.4 Hz), 3.64 (2H, brs), 7.13 (2H, d, J = 7.9 Hz), 7.22 (2H, d, J = 7.9 Hz).

Example 33

({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)acetic acid dihydrochloride

1) To a solution (10 mL) of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (510 mg, 1.24 mmol) in N,N-dimethylformamide were added benzyl bromoacetate (568 mg, 2.48 mmol) and potassium carbonate (343 mg, 2.48 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give 2-(benzyloxy)-2-oxoethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (690 mg, yield 99%) as an oil.

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.14-2.26 (1H, m), 2.36 (3H, s), 2.59 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 4.11-4.17 (2H, m), 4.22 (1H, brs), 4.40 (2H, s), 5.16 (2H, s), 7.05 (2H, d, J = 8.1 Hz), 7.17 (2H, d, J = 7.9 Hz), 7.29-

7.39 (5H, m).

2) A mixture of 2-(benzyloxy)-2-oxoethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (690 mg, 1.23 mmol), palladium-carbon (10%, dry) (132 mg, 0.124 mmol) and ethanol (10 mL) was stirred under a hydrogen atmosphere at room temperature for 30 min. After filtration, the solvent was evaporated under reduced pressure to give ({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)acetic acid as a crude product (580 mg).

^{1}H-NMR ($CDCl_3$) δ:0.96 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.37 (3H, s), 2.62 (3H, s), 2.81 (2H, d, J = 7.0 Hz), 4.11-4.17 (2H, m), 4.30 (1H, brs), 4.36 (2H, s), 7.06 (2H, d, J = 7.7 Hz), 7.19 (2H, d, J = 7.7 Hz).

3) ({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)acetic acid dihydrochloride (517 mg, yield 94%) was obtained as a white powder from the crude product (580 mg) obtained in the aforementioned 2) according to a method similar to the method of Example 2-3).

^{1}H-NMR (CD_3OD) δ:1.11 (6H, d, J = 6.6 Hz), 2.15-2.27 (1H, m), 2.45 (3H, s), 2.94 (3H, s), 3.11 (2H, d, J = 7.5 Hz), 4.20 (2H, s), 4.50 (2H, s), 7.30 (2H, d, J = 8.1 Hz), 7.42 (2H, d, J = 7.9 Hz).

Example 34

2-amino-2-oxoethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate

1) To a solution (10 mL) of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (500 mg, 1.22 mmol) in N,N-dimethylformamide were added 2-iodoacetamide (673 mg, 3.64 mmol) and potassium carbonate (337 mg, 2.44 mmol) and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate (100 mL) and

washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give 2-amino-2-oxoethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (570 mg, yield 99%) as an oil.
^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.17-2.31 (1H, m), 2.39 (3H, s), 2.57 (3H, s), 2.80 (2H, d, J = 7.2 Hz), 4.13-4.18 (2H, m), 4.23 (1H, brs), 4.40 (2H, s), 5.12 (2H, brs), 7.12 (2H, d, J = 7.7 Hz), 7.25 (2H, d, J = 7.9 Hz).
2) 2-Amino-2-oxoethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (370 mg, yield 82%) was obtained as an oil from 2-amino-2-oxoethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (570 mg, 1.21 mmol) according to a method similar to the method of Example 8-3).
^{1}H-NMR ($CDCl_3$) δ:0.99 (6H, d, J = 6.6 Hz), 2.17-2.32 (1H, m), 2.40 (3H, s), 2.57 (3H, s), 2.82 (2H, d, J = 7.2 Hz), 3.70 (2H, s), 4.39 (2H, s), 5.20 (2H, brs), 7.19 (2H, d, J = 8.1 Hz), 7.27 (2H, d, J = 7.9 Hz).

Example 35

4-ethoxy-4-oxobutyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) A mixture of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.41 g, 1.0 mmol), ethyl 4-bromobutyrate (0.21 g, 1.1 mmol), potassium carbonate (0.15 g, 1.1 mmol) and N,N-dimethylformamide (20 mL) was stirred at room temperature for 1 hr., and the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed successively with water and saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give 4-ethoxy-4-oxobutyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-

methyl-4-(4-methylphenyl)nicotinate (0.45 g, yield 85%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.25 (3H, t, J = 7.2 Hz), 1.39 (9H, s), 1.55-1.70 (2H, m), 2.08 (2H, t, J = 7.5 Hz), 2.15-2.30 (1H, m), 2.38 (3H, s), 2.54 (3H, s), 2.78 (2H, d, J = 7.3 Hz), 3.95 (2H, t, J = 6.2 Hz), 4.11 (2H, q, J = 7.2 Hz), 4.53 (2H, d, J = 5.3 Hz), 4.23 (1H, brs), 7.07 (2H, d, J = 8.0 Hz), 7.21 (2H, d, J = 8.0 Hz).

2) 4-Ethoxy-4-oxobutyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (0.12 g, yield 95%) was obtained as a white powder from 4-ethoxy-4-oxobutyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.13 g, 0.25 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.96 (6H, d, J = 6.6 Hz), 1.17 (3H, t, J = 7.2 Hz), 1.45-1.60 (2H, m), 2.05 (2H, t, J = 7.4 Hz), 2.15-2.30 (1H, m), 2.36 (3H, s), 2.51 (3H, brs), 2.85 (2H, t, J = 6.3 Hz), 3.82 (2H, d, J = 5.7 Hz), 3.92 (2H, t, J = 6.3 Hz), 4.03 (2H, q, J = 7.2 Hz), 7.19 (2H, d, J = 7.9 Hz), 7.28 (2H, d, J = 7.9 Hz), 8.21 (3H, brs).

melting point: 193-195°C

Example 36

4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)butanoic acid dihydrochloride

1) 4-Ethoxy-4-oxobutyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.30 g, 0.57 mmol) was dissolved in ethanol (20 mL) and 1N aqueous sodium hydroxide solution (4.0 mL) was added. The mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into 0.5N hydrochloric acid (20 mL) and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and

the obtained crude crystals were recrystallized from diisopropyl ether-ethyl acetate to give 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)butanoic acid (0.23 g, yield 82%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:1.02 (6H, d, J = 6.4 Hz), 1.39 (9H, s), 1.55-1.70 (2H, m), 2.12 (2H, t, J = 7.1 Hz), 2.15-2.30 (1H, m), 2.39 (3H, s), 2.75 (3H, brs), 2.85-3.20 (2H, m), 4.00 (2H, t, J = 6.2 Hz), 4.20 (2H, d, J = 3.6 Hz), 4.37 (1H, brs), 7.10 (2H, d, J = 7.7 Hz), 7.26 (2H, d, J = 7.7 Hz).

2) 4-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)butanoic acid dihydrochloride (0.20 g, yield 99%) was obtained as a white powder from 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)butanoic acid (0.20 g, 0.40 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.97 (6H, d, J = 6.6 Hz), 1.40-1.55 (2H, m), 2.00 (2H, t, J = 7.4 Hz), 2.15-2.30 (1H, m), 2.36 (3H, s), 2.52 (3H, brs), 2.80-2.95 (2H, m), 3.83 (2H, d, J = 4.3 Hz), 3.92 (2H, t, J = 6.2 Hz), 7.20 (2H, d, J = 7.7 Hz), 7.29 (2H, d, J = 7.7 Hz), 8.29 (3H, brs).

melting point: 221-223°C

Example 37

pyridin-2-ylmethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate trihydrochloride

1) To a solution (15 mL) of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.00 g, 2.42 mmol) in N,N-dimethylformamide were added 2-(bromomethyl)pyridine hydrobromide (0.92 g, 3.64 mmol) and potassium carbonate (66.9 mg, 4.84 mmol), and the mixture was stirred for 30 min. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated brine. The organic layer was dried over

anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give pyridin-2-ylmethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.20 g, yield 98%) as a pale-pink solid.

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.14-2.25 (1H, m), 2.35 (3H, s), 2.56 (3H, s), 2.78 (2H, d, J = 7.2 Hz), 4.14 (2H, brs), 4.25 (1H, brs), 5.06 (2H, s), 6.89 (1H, d, J = 7.7 Hz), 7.06 (2H, d, J = 7.9 Hz), 7.13 (2H, d, J = 7.9 Hz), 7.17-7.22 (1H, m), 7.57 (1H, t, J = 7.7 Hz), 8.52 (1H, d, J = 4.7 Hz).

2) Pyridin-2-ylmethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate trihydrochloride (1.22 g, yield 99%) was obtained as a pale-pink solid from pyridin-2-ylmethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.20 g, 2.38 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.97 (6H, d, J = 6.4 Hz), 2.17-2.28 (1H, m), 2.34 (3H, s), 2.61 (3H, s), 2.94 (2H, d, J = 6.8 Hz), 3.81 (2H, d, J = 4.9 Hz), 5.20 (2H, s), 7.19 (4H, s), 7.23 (1H, brs), 7.62-7.66 (1H, m), 8.06 (1H, t, J = 7.9 Hz), 8.39 (3H, brs), 8.68 (1H, d, J = 4.9 Hz).

Example 38

2-ethoxy-1-methyl-2-oxoethyl 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate dihydrochloride

1) 2-Ethoxy-1-methyl-2-oxoethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate (0.35 g, yield 56%) was obtained as a white powder from 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid (0.5 g, 1.2 mmol) and ethyl 2-bromopropionate (0.43 g, 2.4 mmol) according to a method similar to the method of Example 33-1).

^{1}H-NMR ($CDCl_3$) δ:1.02 (9H, s), 1.11 (3H, d, J = 7.0 Hz), 1.25

(3H, t, J = 7.1 Hz), 1.37 (9H, s), 2.38 (3H, s), 2.62 (3H, d, J = 4.9 Hz), 2.83-2.93 (2H, m), 4.17 (2H, q, J = 7.0 Hz), 4.21 (3H, s), 4.82 (1H, q, J = 7.1 Hz), 7.04-7.12 (2H, m), 7.19-7.21 (2H, m).

2) 2-Ethoxy-1-methyl-2-oxoethyl 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate dihydrochloride (0.16 g, yield 85%) was obtained as a white powder from 2-ethoxy-1-methyl-2-oxoethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate (0.2 g, 0.38 mmol) according to a method similar to the method of Example 22-2).

^{1}H-NMR (DMSO-d_6) δ:1.02 (9H, s), 1.06 (3H, d, J = 7.0 Hz), 1.16 (3H, t, J = 7.1 Hz), 2.37 (3H, s), 2.58 (3H, s), 2.95 (2H, s), 3.88 (2H, s), 4.11 (2H, q, J = 7.0 Hz), 4.77 (1H, q, J = 7.1 Hz) 7.13-7.16 (1H, m), 7.23-7.32 (3H, m), 8.24 (3H, s).

Example 39

(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate dihydrochloride

1) (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate (0.9 g, yield 73%) was obtained as a white powder from 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid (1.0 g, 2.3 mmol) and 4-chloromethyl-5-methyl-1,3-dioxol-2-one (0.42 g, 2.8 mmol) according to a method similar to the method of Example 33-1).

^{1}H-NMR ($CDCl_3$) δ:1.01 (9H, s) 1.36 (9H, s), 1.97 (3H, s), 2.39 (3H, s), 2.53 (3H, s), 2.88 (2H, s), 4.16 (3H, s), 4.74 (2H, s), 7.02 (2H, d, J = 7.8 Hz), 7.17 (2H, d, J = 7.8 Hz).

2) To a solution (2 mL) of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate (0.8 g, 1.5 mmol) in ethyl acetate was added 4N hydrogen chloride ethyl acetate solution (8 mL) and the mixture was stirred at room temperature for 4 hrs. The reaction mixture was concentrated under reduced

pressure and the obtained white solid was recrystallized from methanol-ethyl acetate to give (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate dihydrochloride (0.6 g, yield 77%) as a white powder.

^{1}H-NMR (DMSO-d_6) δ:1.00 (9H, s), 1.99 (3H, s), 2.34 (3H, s), 2.52 (3H, s), 2.93 (2H, s), 3.83 (2H, d, J = 5.5 Hz), 4.93 (2H, s), 7.13 (2H, d, J = 7.9 Hz), 7.20 (2H, d, J = 7.9 Hz), 8.18 (3H, s).

Example 40

5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid hemifumarate (to be sometimes referred to as bis[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid] fumarate in this specification)

1) A mixed solution of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (53.7 g, 130 mmol) and 4N hydrogen chloride 1,4-dioxane solution (400 mL) was stirred at room temperature for 3 hrs. The precipitated solid was collected by filtration and washed with diisopropyl ether (200 mL). The obtained white solid was dissolved in isopropanol (500 mL) and the mixture was stirred at 50°C for 30 min. The obtained mixture was allowed to cool to room temperature, and the mixture was stirred at room temperature for 1 hr. The precipitated solid was collected by filtration and washed with isopropanol (50 mL) to give 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid dihydrochloride propan-2-ol solvate (1:1) (46.5 g, yield 80%) as a white solid.

^{1}H-NMR (DMSO-d_6) δ:0.97 (6H, d, J = 6.6 Hz), 1.04 (6H, d, J = 6.0 Hz), 2.16-2.27 (1H, m), 2.37 (3H, s), 2.58 (3H, s), 2.90 (2H, d, J = 7.0 Hz), 3.73-3.86 (3H, m), 7.23 (2H, d, J = 8.1 Hz), 7.30 (2H, d, J = 7.9 Hz), 8.26 (3H, brs).

2) 5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid dihydrochloride propan-2-ol solvate

(1:1) (35.6 g, 80 mmol) was suspended in water (80 mL) and 1N aqueous sodium hydroxide soluti n (160 mL, 160 mmol) was added at room temperature. The mixture was stirred for 1 hr. The precipitated solid was collected by filtration and washed with ethanol (10 mL) to give 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (13.3 g, yield 53%) as a white solid.

^{1}H-NMR (DMSO-d_6) δ:0.93 (6H, d, J = 6.8 Hz), 2.14-2.25 (1H, m), 2.34 (3H, s), 2.38 (3H, s), 2.70 (2H, d, J = 7.2 Hz), 3.49 (2H, s), 7.14-7.20 (4H, m).

3) 5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (15.4 g, 49.3 mmol) was suspended in water (400 mL) and the mixture was heated under reflux with stirring for 30 min. Fumaric acid (3.43 g, 29.6 mmol) was added to the obtained suspension and the mixture was stirred at room temperature for 1 hr. The precipitated solid was collected by filtration and the filtrate was washed with water (50 mL) to give 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid hemifumarate (13.9 g, yield 76%) as white crystals.

^{1}H-NMR (DMSO-d_6) δ:0.93 (6H, d, J = 6.6 Hz), 2.26-2.28 (1H, m), 2.35 (3H, s), 2.42 (3H, s), 2.72 (2H, d, J = 7.2 Hz), 3.55 (2H, s), 6.49 (1H, s), 7.17 (2H, d, J = 8.3 Hz), 7.21 (2H, d, J = 8.3 Hz).

Example 41

3-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]propionamide dihydrochloride

A mixture of tert-butyl {[5-[(1E)-3-amino-3-oxoprop-1-en-1-yl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (97.6 mg, 0.223 mmol), 10% palladium-carbon (24 mg, 0.0223 mmol) and ethanol (5 mL) was stirred under a hydrogen atmosphere at room temperature for 16 hrs. After filtration, the solvent was evaporated under reduced pressure to give tert-butyl {[5-(3-amino-3-oxopropyl)-2-isobutyl-6-

methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate as a crude product. The crude product was dissolved in 4N hydrogen chloride 1,4-dioxane solution (10 mL) and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the obtained white solid was washed with diisopropyl ether to give 3-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]propionamide dihydrochloride (72.7 mg, yield 79%) as a white powder.

^{1}H-NMR (CD_3OD) δ:1.09 (6H, d, J = 6.2 Hz), 2.07-2.19 (1H, m), 2.24-2.29 (2H, m), 2.48 (3H, s), 2.84 (2H, t, J = 7.8 Hz), 2.90 (3H, s), 3.06 (2H, d, J = 7.7 Hz), 4.04 (2H, s), 7.29 (2H, d, J = 7.9 Hz), 7.50 (2H, d, J = 7.7 Hz).

Example 42

ethyl 3-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]propionate dihydrochloride

1) A mixture of ethyl (2E)-3-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acrylate (700 mg, 1.50 mmol), 10% palladium-carbon (160 mg, 0.15 mmol) and ethanol (15 mL) was stirred under a hydrogen atmosphere at room temperature for 1 hr. After filtration, the solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give ethyl 3-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]propionate (480 mg, yield 68%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:0.96 (6H, d, J = 6.6 Hz), 1.18 (3H, t, J = 7.2 Hz), 1.38 (9H, s), 2.11-2.30 (3H, m), 2.40 (3H, s), 2.57 (3H, s), 2.62-2.68 (2H, m), 2.72 (2H, d, J = 7.4 Hz), 3.96-4.07 (4H, m), 4.18 (1H, brs), 6.98 (2H, d, J = 7.91), 7.24 (2H, d, J = 7.9 Hz).

2) Ethyl 3-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]propionate dihydrochloride (58.3 mg, yield 85%) was obtained as a white powder from ethyl 3-[5-

{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]pr pi nate (73.0 mg, 0.156 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (CD_3OD) δ:1.08 (6H, d, J = 6.6 Hz), 1.17 (3H, t, J = 7.2 Hz), 2.08-2.21 (1H, m), 2.34-2.39 (2H, m), 2.48 (3H, s), 2.82-2.85 (2H, m), 2.88 (3H, s), 3.05 (2H, d, J = 7.5 Hz), 4.00-4.07 (4H, m), 7.27 (2H, d, J = 7.9 Hz), 7.50 (2H, d, J = 7.9 Hz).

Example 43

3-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]propionic acid dihydrochloride

1) To a mixed solution (10 mL) of ethyl 3-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]propionate (407 mg, 0.868 mmol) in tetrahydrofuran was added 1N aqueous sodium hydroxide solution (4.30 mL, 4.30 mmol) and the mixture was stirred at 50°C for 5 hrs. The reaction mixture was neutralized with 6N hydrochloric acid (0.8 mL) and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give 3-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]propionic acid (255 mg, yield 60%) as a yellow powder.

^{1}H-NMR (CD_3OD) δ:1.04 (6H, d, J = 6.6 Hz), 2.05-2.17 (1H, m), 2.26-2.36 (2H, m), 2.44 (3H, s), 2.75-2.87 (5H, m), 2.97 (2H, d, J = 7.5 Hz), 4.05 (2H, s), 7.17 (2H, d, J = 8.1 Hz), 7.40 (2H, d, J = 7.7 Hz).

2) 3-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]propionic acid dihydrochloride (94.2 mg, yield 97%) was obtained as a white powder from 3-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]propionic acid (100 mg, 0.234 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (CD_3OD) δ:1.09 (6H, d, J = 6.6 Hz), 2.09-2.22 (1H, m), 2.30-2.38 (2H, m), 2.48 (3H, s), 2.80-2.88 (2H, m), 2.90 (3H, s), 3.05 (2H, d, J = 7.5 Hz), 4.05 (2H, s), 7.26 (2H, d, J = 7.9 Hz), 7.51 (2H, d, J = 8.1 Hz).

Example 44

2-[5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)-2-propylpyridin-3-yl]acetamide

1) tert-Butyl{[5-(hydroxymethyl)-2-isobutyl-4-(4-methylphenyl)-6-propylpyridin-3-yl]methyl}carbamate (1.40 g, yield 60%) was obtained as a pale-pink powder from methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)-2-propylnicotinate (2.50 g, 5.50 mmol) according to a method similar to the method of Example 5-1).

^{1}H-NMR ($CDCl_3$) δ:0.96 (6H, d, J = 6.6 Hz), 1.02 (3H, d, J = 7.4 Hz), 1.38 (9H, s), 1.73-1.86 (2H, m), 2.14-2.28 (1H, m), 2.41 (3H, s), 2.76 (2H, d, J = 7.2 Hz), 2.88-2.93 (2H, m), 4.04 (2H, d, J = 5.1 Hz), 4.20 (1H, brs), 4.36 (2H, d, J = 5.8 Hz), 7.06 (2H, d, J = 7.9 Hz), 7.26 (2H, d, J = 7.35 Hz).

2) tert-Butyl {[5-(cyanomethyl)-2-isobutyl-4-(4-methylphenyl)-6-propylpyridin-3-yl]methyl}carbamate (0.82 g, yield 67%) was obtained as an oil from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-4-(4-methylphenyl)-6-propylpyridin-3-yl]methyl}carbamate (1.20 g, 2.81 mmol) according to a method similar to the method of Example 5-2).

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.05 (3H, t, J = 7.4 Hz), 1.38 (9H, s), 1.78-1.90 (2H, m), 2.18-2.27 (1H, m), 2.43 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 2.81-2.86 (2H, m), 3.33 (2H, s), 4.05-4.06 (2H, m), 4.20 (1H, brs), 7.05 (2H, d, 7.9 Hz), 7.30 (2H, d, J = 7.7 Hz),

3) tert-Butyl {[5-(2-amino-2-oxoethyl)-2-isobutyl-4-(4-methylphenyl)-6-propylpyridin-3-yl]methyl}carbamate (814 mg, yield 95%) was obtained as a white powder from tert-butyl {[5-(cyanomethyl)-2-isobutyl-4-(4-methylphenyl)-6-propylpyridin-3-yl]methyl}carbamate (0.82 g, 1.88 mmol) according to a method

similar to the method of Example 6-1).

^{1}H-NMR (CD_3OD) δ:0.98-1.05 (9H, m), 1.38 (9H, s), 1.66-1.77 (2H, m), 2.08-2.19 (1H, m), 2.39 (3H, s), 2.76-2.80 (4H, m), 3.37 (2H, s), 3.92-3.97 (2H, m), 4.59 (1H, brs), 7.70 (2H, d, J = 8.1 Hz), 7.27 (2H, d, J = 7.7 Hz).

4) 2-[5-(Aminomethyl)-6-isobutyl-4-(4-methylphenyl)-2-propylpyridin-3-yl]acetamide (31 mg, yield 10%) was obtained as an oil from tert-butyl {[5-(2-amino-2-oxoethyl)-2-isobutyl-4-(4-methylphenyl)-6-propylpyridin-3-yl]methyl}carbamate (300 mg, 0.84 mmol) according to a method similar to the method of Example 8-3).

^{1}H-NMR (CD_3OD) δ:0.99 (6H, d, J = 6.6 Hz), 1.01 (3H, t, J = 7.4 Hz), 1.63-1.71 (2H, m), 2.04-2.18 (1H, m), 2.40 (3H, s), 2.71-2.76 (2H, m), 2.79 (2H, d, J = 7.4 Hz), 3.33 (2H, s), 3.53 (2H, s), 7.11 (2H, d, J = 7.9 Hz), 7.30 (2H, d, J = 7.9 Hz).

Example 45

tert-butyl 5-(aminomethyl)-2,6-diisobutyl-4-(4-methylphenyl)nicotinate

1) tert-Butyl 3-amino-5-methylhex-2-enoate was obtained as a crude product (10 g) from Meldrum's acid (14.41 g, 100 mmol) and isovaleryl chloride (11.5 mL, 110 mmol) according to a method similar to the method of Example 25-1).

2) tert-Butyl 5-cyano-2,6-diisobutyl-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (12.11 g, yield 74%) was obtained as an oil from 5-methyl-3-oxohexanenitrile (5.0 g, 40 mmol), p-tolualdehyde (4.8 g, 40 mmol), and the crude product (9.96 g) obtained in the aforementioned 1), according to a method similar to the method of Example 1-2).

3) tert-Butyl 5-cyano-2,6-diisobutyl-4-(4-methylphenyl)nicotinate (3.39 g, yield 83%) was obtained from tert-butyl 5-cyano-2,6-diisobutyl-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (4.09 g, 10 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:0.95 (6H, d, J = 6.6 Hz), 1.00 (6H, d, J = 6.6

Hz), 1.23 (9H, s), 2.19-2.33 (1H, m), 2.41 (3H, s), 2.76 (2H, d, J = 7.5 Hz), 2.94 (2H, d, J = 7.2 Hz), 7.20-7.35 (4H, m).

4) tert-Butyl 5-(aminomethyl)-2,6-diisobutyl-4-(4-methylphenyl)nicotinate (2.85 g, yield 86%) was obtained as an oil from tert-butyl 5-cyano-2,6-diisobutyl-4-(4-methylphenyl)nicotinate (3.25 g, 8 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.93 (6H, d, J = 6.6 Hz), 0.97 (6H, d, J = 6.6 Hz), 1.17 (9H, s), 1.38 (2H, brs), 2.16-2.30 (2H, m), 2.39 (3H, s), 2.67 (2H, d, J = 7.5 Hz), 2.79 (2H, d, J = 7.2 Hz), 3.62 (2H, s), 7.13 (2H, d, J = 8.1 Hz), 7.21 (2H, d, J = 8.1 Hz).

Example 46

5-(aminomethyl)-2,6-diisobutyl-4-(4-methylphenyl)nicotinic acid dihydrochloride

5-(Aminomethyl)-2,6-diisobutyl-4-(4-methylphenyl)nicotinic acid dihydrochloride (0.39 g, yield 92%) was obtained as a white powder from tert-butyl 5-(aminomethyl)-2,6-diisobutyl-4-(4-methylphenyl)nicotinate (0.41 g, 1 mmol) ac ording to a method similar to the method of Example 24-1).

^{1}H-NMR (DMSO-d_6) δ:0.90 (6H, d, J = 6.6 Hz), 0.96 (6H, d, J = 6.6 Hz), 2.16-2.29 (2H, m), 2.37 (3H, s), 2.68 (2H, d, J = 7.2 Hz), 2.88 (2H, d, J = 7.2 Hz), 3.79 (2H, d, J = 5.1 Hz), 7.22 (2H, d, J = 8.1 Hz), 7.29 (2H, d, J = 8.1 Hz), 8.12 (3H, brs).

Example 47

({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]pyridin-3-yl}methyl)amine p-toluenesulfonate

1) To a suspension of sodium p-toluenesulfinate (9.0 g, 50.5 mmol) in ethanol (50 mL) was added dropwise bromoacetone (6.92 g, 50.5 mmol). The obtained mixture was heated under reflux for 30 min., allowed to cool to room temperature and partitioned between ethyl acetate and water. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced

pressure. The residue was purified by silica gel column chromatography to give 1-[(4-methylphenyl)sulfonyl]acetone (8.0 g, yield 75%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ:2.41 (3H, s), 2.46 (3H, s), 4.14 (2H, s), 7.37 (2H, d, J = 8.2 Hz), 7.77 (2H, d, J = 8.2 Hz).

2) A mixture of 1-[(4-methylphenyl)sulfonyl]acetone (2.0 g, 9.4 mmol), p-tolualdehyde (1.14 g, 9.4 mmol), piperidine (0.093 mL, 0.94 mmol), acetic acid (0.11 mL, 1.9 mmol) and toluene (100 mL) was heated under reflux using a Dean-Stark trap for 3 hrs. The reaction mixture was allowed to cool to room temperature, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 4-(4-methylphenyl)-3-[(4-methylphenyl)sulfonyl]but-3-en-2-one as a crude product (3.5 g).

3) A mixture of 5-methyl-3-oxohexanenitrile (14.3 g, 100 mmol), acetic acid (6.0 g, 10 mmol), ammonium acetate (38.5 g, 500 mmol) and toluene (200 mL) was heated under reflux using a Dean-Stark trap for 17 hrs. The reaction mixture was allowed to cool to room temperature, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give 3-amino-5-methylhex-2-enenitrile as a mixture (8.2 g). The mixture (0.65 g) and the crude product (1.7 g) obtained in the aforementioned 2) were dissolved in ethanol (50 mL) and the mixture was heated under reflux for 12 hrs. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to give 2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]-1,4-dihydropyridine-3-carbonitrile (1.3 g, yield 64%) as a white powder.

EIMS (M+1): 421

4) 2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]nicotinonitrile (0.77 g, yield 68%) was

obtained as a white powder from 2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]-1,4-dihydropyridine-3-carbonitrile (1.13 g, 2.7 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:0.99 (6H, d, J = 6.6 Hz), 2.20-2.35 (1H, m), 2.38 (3H, s), 2.39 (3H, s), 2.91 (2H, d, J = 7.2 Hz), 3.07 (3H, s), 6.86 (2H, d, J = 8.1 Hz), 7.08 (4H, d, J = 8.1 Hz), 7.23 (2H, d, J = 8.1 Hz).

melting point: 129-131°C

5) ({2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]pyridin-3-yl}methyl)amine (0.64 g, yield 93%) was obtained as a colorless oil from 2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]nicotinonitrile (0.69 g, 1.6 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.96 (6H, d, J = 6.6 Hz), 1.41 (2H, brs), 2.20-2.35 (1H, m), 2.38 (6H, s), 2.79 (2H, d, J = 7.2 Hz), 2.96 (3H, s), 3.40 (2H, s), 6.76 (2H, d, J = 8.1 Hz), 7.03 (2H, d, J = 8.3 Hz), 7.09 (2H, d, J = 8.1 Hz), 7.27 (2H, d, J = 8.3 Hz).

6) To a solution of ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]pyridin-3-yl}methyl)amine (0.64 g, 1.5 mmol) in ethanol (5 mL) was added dropwise a solution of p-toluenesulfonic acid monohydrate (0.29 g, 1.5 mmol) in ethanol (5 mL) at room temperature. The precipitated crystals were collected by filtration, washed with cold ethanol and dried to give ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]pyridin-3-yl}methyl)amine p-toluenesulfonate (0.57 g, yield 63%) as a white powder.

^{1}H-NMR (DMSO-d_6) δ:0.94 (6H, d, J = 6.6 Hz), 2.15-2.30 (1H, m), 2.29 (3H, s), 2.37 (6H, s), 2.78 (2H, d, J = 7.0 Hz), 2.84 (3H, s), 3.57 (2H, s), 6.87 (2H, d, J = 7.9 Hz), 7.11 (4H, d, J = 8.5 Hz), 7.25-7.30 (4H, m), 7.47 (2H, d, J = 7.9 Hz), 7.76 (3H, brs).

melting point: 234-235°C

Example 48

tert-butyl 5-(aminomethyl)-2-benzyl-6-isobutyl-4-(4-methylphenyl)nicotinate

1) tert-Butyl 3-amino-4-phenylbut-2-enoate was obtained as a crude product (16 g) from Meldrum's acid (14.41 g, 100 mmol) and phenylacetyl chloride (14.5 mL, 110 mmol) according to a method similar to the method of Example 25-1).

2) tert-Butyl 2-benzyl-5-cyano-6-isobutyl-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (14.1 g, yield 79%) was obtained as an oil from 5-methyl-3-oxohexanenitrile (5.0 g, 40 mmol), p-tolualdehyde (4.8 g, 40 mmol), and the crude product (16 g) obtained in the aforementioned 1), according to a method similar to the method of Example 1-2).

3) tert-Butyl 2-benzyl-5-cyano-6-isobutyl-4-(4-methylphenyl)nicotinate (2.92 g, yield 66%) was obtained from tert-butyl 2-benzyl-5-cyano-6-isobutyl-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (4.43 g, 10 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.6 Hz), 1.10 (9H, s), 2.19-2.35 (1H, m), 2.40 (3H, s), 2.94 (2H, d, J = 7.2 Hz), 4.28 (2H, s), 7.16-7.32 (9H, m).

4) tert-Butyl 5-(aminomethyl)-2-benzyl-6-isobutyl-4-(4-methylphenyl)nicotinate (2.45 g, yield 55%) was obtained as an oil from tert-butyl 2-benzyl-5-cyano-6-isobutyl-4-(4-methylphenyl)nicotinate (4.40 g, 10 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.95 (6H, d, J = 6.6 Hz), 1.05 (9H, s), 1.26 (2H, brs), 2.21-2.30 (1H, m), 2.38 (3H, s), 2.79 (2H, d, J = 7.5 Hz), 3.62 (2H, s), 4.20 (2H, s), 7.11-7.31 (9H, m).

Example 49

5-(aminomethyl)-2-benzyl-6-isobutyl-4-(4-methylphenyl)nicotinic acid dihydrochloride

5-(Aminomethyl)-2-benzyl-6-isobutyl-4-(4-methylphenyl)nicotinic acid dihydrochloride (0.38 g, yield 82%)

was obtained as a white powder from tert-butyl 5-(aminomethyl)-2-benzyl-6-isobutyl-4-(4-methylphenyl)nicotinate (0.44 g, 1 mmol) according to a method similar to the method of Example 24-1).

^{1}H-NMR (DMSO-d_6) δ:0.93 (6H, d, J = 6.3 Hz), 2.16-2.29 (1H, m), 2.37 (3H, s), 2.82 (2H, d, J = 6.6 Hz), 3.77 (2H, d, J = 4.8 Hz), 4.13 (2H, s), 7.15-7.31 (9H, m), 8.16 (3H, brs).

Example 50

5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)-2-phenylnicotinic acid dihydrochloride

1) Ethyl 3-amino-3-phenylacrylate was obtained as a crude product (9.5 g) from ethyl 3-oxo-3-phenylpropanoate (9.61 g, 50 mmol) and ammonium acetate (19.27 g, 250 mmol) according to a method similar to the method of Example 12-1).

2) Ethyl 5-cyano-6-isobutyl-4-(4-methylphenyl)-2-phenyl-1,4-dihydropyridine-3-carboxylate (9.52 g, yield 59%) was obtained as an oil from 5-methyl-3-oxohexanenitrile (5.0 g, 40 mmol), p-tolualdehyde (4.8 g, 40 mmol) and the crude product (9.5 g) obtained in the aforementioned 1), according to a method similar to the method of Example 1-2).

3) Ethyl 5-cyano-6-isobutyl-4-(4-methylphenyl)-2-phenylnicotinate (4.11 g, yield 85%) was obtained as an oil from ethyl 5-cyano-6-isobutyl-4-(4-methylphenyl)-2-phenyl-1,4-dihydropyridine-3-carboxylate (4.81 g, 12 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:0.85 (3H, t, J = 7.2 Hz), 1.05 (6H, d, J = 6.6 Hz), 2.29-2.44 (4H, m), 3.05 (2H, d, J = 7.2 Hz), 3.91 (2H, q, J = 7.2 Hz), 7.26-7.33 (4H, m), 7.43-7.48 (3H, m), 7.624-7.69 (2H, m).

4) Ethyl 5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)-2-phenylnicotinate (3.63 g, yield 90%) was obtained as an oil from ethyl 5-cyano-6-isobutyl-4-(4-methylphenyl)-2-phenylnicotinate (4.40 g, 10 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, t, J = 7.2 Hz), 1.03 (6H, d, J = 6.6 Hz), 1.36 (2H, bs), 2.29-2.42 (4H, m), 2.90 (2H, d, J = 7.2 Hz), 3.70 (2H, s), 3.81 (2H, q, J = 7.2 Hz), 7.17 (2H, d, J = 8.1 Hz), 7.23 (2H, d, J = 8.1 Hz), 7.35-7.43 (3H, m), 7.62-7.65 (2H, m).

5) A mixture of ethyl 5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)-2-phenylnicotinate (0.80 g, 2 mmol), 6N hydrochloric acid (20 mL) and acetic acid (10 mL) was heated under reflux for 3 days. The reaction mixture was concentrated under reduced pressure. Tetrahydrofuran (20 mL) and 1N aqueous sodium hydroxide solution (30 mL) were added to the residue. To the obtained mixture was added di-tert-butyl dicarbonate (0.55 mL, 2.4 mmol) and the resulting mixture was stirred at room temperature for 2 hrs. The reaction mixture was acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silicagel column chromatography to give 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)-2-phenylnicotinic acid (0.38 g, 0.8 mmol) as an oil. Then, 5-(Aminomethyl)-6-isobutyl-4-(4-methylphenyl)-2-phenylnicotinic acid dihydrochloride (0.31 g, yield 88%) was obtained as a white powder from the oil according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:1.01 (6H, d, J = 6.6 Hz), 2.24-2.35 (1H, m), 2.38 (3H, s), 2.93 (2H, d, J = 6.9 Hz), 3.82 (2H, d, J = 5.1 Hz), 7.26-7.32 (4H, m), 7.44-7.52 (3H, m), 7.66-7.69 (2H, m), 8.38 (3H, brs).

Example 51

methyl 5-(aminomethyl)-2-ethyl-6-isobutyl-4-(4-methylphenyl)nicotinate

1) Methyl 3-aminopent-2-enoate was obtained as a crude product (6.4 g) from methyl 3-oxopentaneoate (6.50 g, 50 mmol) and

ammonium acetate (19.27 g, 250 mmol) according to a method similar to the method of Example 12-1).

2) Methyl 5-cyano-2-ethyl-6-isobutyl-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (4.12 g, yield 48%) was obtained as an oil from 5-methyl-3-oxohexanenitrile (5.0 g, 40 mmol), p-tolualdehyde (4.8 g, 40 mmol) and the crude product (3.2 g) obtained in the aforementioned 1), according to a method similar to the method of Example 1-2).

3) Methyl 5-cyano-2-ethyl-6-isobutyl-4-(4-methylphenyl)nicotinate (3.41 g, yield 84%) was obtained from methyl 5-cyano-2-ethyl-6-isobutyl-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (4.06 g, 12 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:1.01 (6H, d, J = 6.6 Hz), 1.32 (3H, t, J = 7.5 Hz), 2.24-2.36 (1H, m), 2.41 (3H, s), 2.85 (2H, q, J = 7.5 Hz), 2.96 (2H, d, J = 6.9 Hz), 3.59 (3H, s), 7.24-7.30 (4H, m).

4) Methyl 5-(aminomethyl)-2-ethyl-6-isobutyl-4-(4-methylphenyl)nicotinate (2.49 g, yield 73%) was obtained as a white powder from methyl 5-cyano-2-ethyl-6-isobutyl-4-(4-methylphenyl)nicotinate (4.40 g, 10 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.6 Hz), 1.29 (3H, t, J = 7.5 Hz), 2.18-2.31 (1H, m), 2.34 (3H, s), 2.77 (2H, q, J = 7.5 Hz), 2.81 (2H, d, J = 7.2 Hz), 3.49 (3H, s), 3.65 (2H, s), 7.11 (2H, d, J = 8.0 Hz), 7.21 (2H, d, J = 8.0 Hz).

Example 52

5-(aminomethyl)-2-ethyl-6-isobutyl-4-(4-methylphenyl)nicotinic acid dihydrochloride

5-(Aminomethyl)-2-ethyl-6-isobutyl-4-(4-methylphenyl)nicotinic acid dihydrochloride (0.30 g, yield 82%) was obtained as a white powder from methyl 5-(aminomethyl)-2-ethyl-6-isobutyl-4-(4-methylphenyl)nicotinate (0.34 g, 1 mmol) according to a method similar to the method of Example 50-5).

^{1}H-NMR (DMSO-d_6) δ:0.97 (6H, d, J = 6.6 Hz), 1.26 (3H, t, J =

7.5 Hz), 2.17-2.26 (1H, m), 2.37 (3H, s), 2.89 (2H, q, J = 7.3 Hz), 3.00 (2H, d, J = 6.9 Hz), 3.81 (2H, d, J = 6.0 Hz), 7.25 (2H, d, J = 8.2 Hz), 7.30 (2H, d, J = 8.2 Hz), 8.38 (3H, brs).

Example 53

5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid maleate

To a mixed solution of 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid (114 mg, 0.350 mmol), acetonitrile (2 mL) and water (2 mL) was added maleic acid (40.6 mg, 0.350 mmol) and the mixture was stirred at room temperature. After dissolution of maleic acid, acetonitrile (8 mL) was added, and the mixture was stirred at room temperature for 1 hr. The obtained solution was concentrated under reduced pressure, and acetonitrile (10 mL) was added to the residue. The mixture was stirred at room temperature for 1 hr. The precipitated crystals were collected by filtration to give 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid maleate (92.6 mg, 60%) as colorless powder crystals.
^{1}H-NMR (DMSO-d_6) δ:1.00 (9H, s), 2.36 (3H, s), 2.49 (3H, s), 2.81 (2H, s), 3.84 (2H, s), 6.01 (2H, s), 7.17-7.21 (2H, m), 7.27-7.31 (2H, m).

Example 54

5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid tartarate

To a mixed solution of 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid (114 mg, 0.350 mmol), acetonitrile (2 mL) and water (2 mL) was added tartaric acid (40.6 mg, 0.350 mmol), and the mixture was stirred at room temperature. After dissolution of tartaric acid, acetonitrile (8 mL) was added, and the mixture was stirred at room temperature for 1 hr. The obtained solution was concentrated under reduced pressure, and acetonitrile (10 mL) was added to the residue. The mixture was stirred at room temperature for 1 hr. The precipitated crystals were collected by filtration to

give 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid tartarate (129 mg, 77%) as colorless powder crystals.

^{1}H-NMR (DMSO-d_6) δ:0.98 (9H, s), 2.35 (3H, s), 2.44 (3H, s), 2.79 (2H, s), 3.75 (2H, s), 3.96 (2H, s), 7.15-7.19 (2H, m), 7.21-7.25 (2H, m).

Example 55

tert-butyl 5-(aminomethyl)-2-isobutyl-4-(4-methylphenyl)-6-neopentylnicotinate

1) tert-Butyl 3-amino-5-methylhex-2-enoate was obtained as a crude product (10 g) from Meldrum's acid (14.41 g, 100 mmol) and isovaleryl chloride (11.5 mL, 110 mmol) according to a method similar to the method of Example 25-1).

2) tert-Butyl 5-cyano-2-isobutyl-4-(4-methylphenyl)-6-neopentyl-1,4-dihydropyridine-3-carboxylate (3.75 g, yield 22%) was obtained as an oil from 5,5-dimethyl-3-oxohexanenitrile (5.57 g, 40 mmol), p-tolualdehyde (4.81 g, 40 mmol) and the crude product (10 g) obtained in the aforementioned 1), according to a method similar to the method of Example 1-2).

3) tert-Butyl 5-cyano-2-isobutyl-4-(4-methylphenyl)-6-neopentylnicotinate (1.66 g, yield 49%) was obtained from tert-butyl 5-cyano-2-isobutyl-4-(4-methylphenyl)-6-neopentyl-1,4-dihydropyridine-3-carboxylate (3.38 g, 10 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:0.95 (6H, d, J = 6.6 Hz), 1.06 (9H, s), 1.24 (9H, s), 2.22-2.35 (1H, m), 2.40 (3H, s), 2.76 (2H, d, J = 7.2 Hz), 3.00 (2H, s), 7.19-7.35 (4H, m).

4) tert-Butyl 5-(aminomethyl)-2-isobutyl-4-(4-methylphenyl)-6-neopentylnicotinate (1.34 g, yield 89%) was obtained as white crystals from tert-butyl 5-cyano-2-isobutyl-4-(4-methylphenyl)-6-neopentylnicotinate (3.25 g, 8 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.93 (6H, d, J = 6.6 Hz), 1.02 (9H, s), 1.17 (9H, s), 1.24 (2H, brs), 2.22-2.31 (1H, m), 2.39 (3H, s), 2.66

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(2H, d, J = 7.5 Hz), 2.87 (2H, s), 3.68 (2H, s), 7.13 (2H, d, J = 8.0 Hz), 7.21 (2H, d, J = 8.0 Hz).

Example 56

tert-butyl 5-(aminomethyl)-2-benzyl-4-(4-methylphenyl)-6-neopentylnicotinate

1) tert-Butyl 3-amino-4-phenylbut-2-enoate was obtained as a crude product (16 g) from Meldrum's acid (14.41 g, 100 mmol) and phenylacetyl chloride (14.5 mL, 110 mmol) according to a method similar to the method of Example 25-1).

2) tert-Butyl 2-benzyl-5-cyano-4-(4-methylphenyl)-6-neopentyl-1,4-dihydropyridine-3-carboxylate (12.5 g, yield 68%) was obtained as an oil from 5,5-dimethyl-3-oxohexanenitrile (5.57 g, 40 mmol), p-tolualdehyde (4.81 g, 40 mmol), and the crude product (11.6 g) obtained in the aforementioned 1), according to a method similar to the method of Example 1-2).

3) tert-Butyl 2-benzyl-5-cyano-4-(4-methylphenyl)-6-neopentylnicotinate (6.8 g, yield 100%) was obtained from tert-butyl 2-benzyl-5-cyano-4-(4-methylphenyl)-6-neopentyl-1,4-dihydropyridine-3-carboxylate (6.8 g, 10 mmol) according to a method similar to the method of Example 23-3).

4) tert-Butyl 5-(aminomethyl)-2-benzyl-4-(4-methylphenyl)-6-neopentylnicotinate (0.48 g, yield 15%) was obtained as white crystals from tert-butyl 2-benzyl-5-cyano-4-(4-methylphenyl)-6-neopentylnicotinate (3.18 g, 7 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.96 (9H, s), 1.07 (9H, s), 2.39 (3H, s), 2.85 (2H, s), 3.67 (2H, s), 4.18 (2H, s), 7.11-7.32 (9H, m).

Example 57

tert-butyl 5-(aminomethyl)-2-ethyl-4-(4-methylphenyl)-6-neopentylnicotinate

1) tert-Butyl 3-aminopent-2-enoate was obtained as a crude product (8.5 g) from Meldrum's acid (14.41 g, 100 mmol) and propionyl chloride (9.6 mL, 110 mmol) according to a method similar to the method of Example 25-1).

2) tert-Butyl 5-cyano-2-ethyl-4-(4-methylphenyl)-6-neopentyl-1,4-dihydropyridine-3-carboxylate (6.0 g, yield 38%) was obtained as an oil from 5,5-dimethyl-3-oxohexanenitrile (5.57 g, 40 mmol), p-tolualdehyde (4.81 g, 40 mmol) and the crude product (8.5 g) obtained in the aforementioned 1), according to a method similar to the method of Example 1-2).

3) tert-Butyl 5-cyano-2-ethyl-4-(4-methylphenyl)-6-neopentylnicotinate (2.58 g, yield 43%) was obtained as a pale-yellow solid from tert-butyl 5-cyano-2-ethyl-4-(4-methylphenyl)-6-neopentyl-1,4-dihydropyridine-3-carboxylate (5.92 g, 15 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:1.07 (9H, s), 1.26 (9H, s), 1.34 (3H, t, J = 7.5 Hz), 2.41 (3H, s), 2.89 (2H, q, J = 7.5 Hz), 3.01 (2H, s), 7.20-7.29 (4H, m).

4) tert-Butyl 5-(aminomethyl)-2-ethyl-4-(4-methylphenyl)-6-neopentylnicotinate (1.56 g, yield 65%) was obtained as an oil from tert-butyl 5-cyano-2-ethyl-4-(4-methylphenyl)-6-neopentylnicotinate (2.36 g, 6 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:1.03 (9H, s), 1.19 (9H, s), 1.28 (2H, brs), 1.32 (3H, t, J = 7.5 Hz), 2.39 (3H, s), 2.80 (2H, q, J = 7.5 Hz), 2.87 (2H, s), 3.68 (2H, s), 7.13 (2H, d, J = 8.1 Hz), 7.21 (2H, d, J = 8.1 Hz).

Example 58

5-(aminomethyl)-2-ethyl-4-(4-methylphenyl)-6-neopentylnicotinic acid dihydrochloride

5-(Aminomethyl)-2-ethyl-4-(4-methylphenyl)-6-neopentylnicotinic acid dihydrochloride (0.37 g, yield 90%) was obtained as a white powder from tert-butyl 5-(aminomethyl)-2-ethyl-4-(4-methylphenyl)-6-neopentylnicotinate (0.39 g, 1 mmol) according to a method similar to the method of Example 24-1).

^{1}H-NMR (DMSO-d_6) δ:1.02 (9H, s), 1.26 (3H, t, J = 7.5 Hz), 2.37 (3H, s), 2.78 (2H, q, J = 7.5 Hz), 2.92 (2H, s), 3.83 (2H, d, J

= 5.4 Hz), 7.21 (2H, d, J = 8.0 Hz), 7.29 (2H, d, J = 8.0 Hz), 8.13 (3H, brs).

Example 59

tert-butyl 5-(aminomethyl)-4-(4-methylphenyl)-6-neopentyl-2-propylnicotinate

1) tert-Butyl 3-aminohex-2-enoate was obtained as a crude product (9.2 g) from Meldrum's acid (14.41 g, 100 mmol) and butyryl chloride (11.4 mL, 110 mmol) according to a method similar to the method of Example 25-1).

2) tert-Butyl 5-cyano-4-(4-methylphenyl)-6-neopentyl-2-propyl-1,4-dihydropyridine-3-carboxylate (10.1 g, yield 61%) was obtained as an oil from 5,5-dimethyl-3-oxohexanenitrile (5.57 g, 40 mmol), p-tolualdehyde (4.81 g, 40 mmol) and the crude product (16 g) obtained in the aforementioned 1), according to a method similar to the method of Example 1-2).

3) tert-Butyl 5-cyano-4-(4-methylphenyl)-6-neopentyl-2-propylnicotinate (5.74 g, yield 58%) was obtained as an oil from tert-butyl 5-cyano-4-(4-methylphenyl)-6-neopentyl-2-propyl-1,4-dihydropyridine-3-carboxylate (9.8 g, 24 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:1.00 (3H, t, J = 7.5 Hz), 1.06 (9H, s), 1.26 (9H, s), 1.75-1.88 (2H, m), 2.41 (3H, s), 2.81-2.86 (2H, m), 3.00 (2H, s), 7.18-7.30 (4H, m).

4) tert-Butyl 5-(aminomethyl)-4-(4-methylphenyl)-6-neopentyl-2-propylnicotinate (3.36 g, yield 74%) was obtained as white crystals from tert-butyl 5-cyano-4-(4-methylphenyl)-6-neopentyl-2-propylnicotinate (4.47 g, 11 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.98 (3H, t, J = 7.3 Hz), 1.02 (9H, s), 1.14 (2H, brs), 1.14 (9H, s), 1.73-1.86 (2H, m), 2.39 (3H, s), 2.72-2.77 (2H, m), 2.87 (2H, s), 3.68 (2H, s), 7.13 (2H, d, J = 8.1 Hz), 7.21 (2H, d, J = 8.1 Hz).

Example 60

5-(aminomethyl)-4-(4-methylphenyl)-6-neopentyl-2-

propylnicotinic acid dihydrochloride

5-(Aminomethyl)-4-(4-methylphenyl)-6-neopentyl-2-propylnicotinic acid dihydrochloride (0.38 g, yield 90%) was obtained as a white powder from tert-butyl 5-(aminomethyl)-4-(4-methylphenyl)-6-neopentyl-2-propylnicotinate (0.41 g, 1 mmol) according to a method similar to the method of Example 24-1).

^{1}H-NMR (DMSO-d_6) δ:0.93 (3H, t, J = 7.3 Hz), 1.02 (9H, s), 1.69-1.81 (2H, m), 2.37 (3H, s), 2.74-2.79 (2H, m), 2.94 (2H, brs), 3.84 (2H, d, J = 5.1 Hz), 7.22 (2H, d, J = 8.0 Hz), 7.29 (2H, d, J = 8.0 Hz), 8.14 (3H, brs).

Example 61

tert-butyl 5-(aminomethyl)-2-isopropyl-4-(4-methylphenyl)-6-neopentylnicotinate

1) tert-Butyl 3-amino-4-methylpent-2-enoate was obtained as a crude product (9.2 g) from Meldrum's acid (14.41 g, 100 mmol) and isobutyryl chloride (11.4 mL, 110 mmol) according to a method similar to the method of Example 25-1).

2) tert-Butyl 5-cyano-2-isopropyl-4-(4-methylphenyl)-6-neopentyl-1,4-dihydropyridine-3-carboxylate (4.91 g, yield 30%) was obtained as an oil from 5,5-dimethyl-3-oxohexanenitrile (5.57 g, 40 mmol), p-tolualdehyde (4.81 g, 40 mmol) and the crude product (9.2 g) obtained in the aforementioned 1), according to a method similar to the method of Example 1-2).

3) tert-Butyl 5-cyano-2-isopropyl-4-(4-methylphenyl)-6-neopentylnicotinate (2.48 g, yield 50%) was obtained from tert-butyl 5-cyano-2-isopropyl-4-(4-methylphenyl)-6-neopentyl-1,4-dihydropyridine-3-carboxylate (4.90 g, 12 mmol) according to a method similar to the method of Example 23-3).

4) tert-Butyl 5-(aminomethyl)-2-isopropyl-4-(4-methylphenyl)-6-neopentylnicotinate (1.26 g, yield 51%) was obtained as white crystals from tert-butyl 5-cyano-2-isopropyl-4-(4-methylphenyl)-6-neopentylnicotinate (3.25 g, 8 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:1.04 (9H, s), 1.18 (9H, s), 1.30 (6H, d, J = 6.9 Hz), 1.32 (2H, brs), 2.39 (3H, s), 2.85 (2H, s), 3.04-3.13 (1H, m), 3.66 (2H, s), 7.13 (2H, d, J = 8.0 Hz), 7.20 (2H, d, J = 8.0 Hz).

Example 62

5-(aminomethyl)-2-isopropyl-4-(4-methylphenyl)-6-neopentylnicotinic acid dihydrochloride

5-(Aminomethyl)-2-isopropyl-4-(4-methylphenyl)-6-neopentylnicotinic acid dihydrochloride (0.37 g, yield 88%) was obtained as a white powder from tert-butyl 5-(aminomethyl)-2-isopropyl-4-(4-methylphenyl)-6-neopentylnicotinate (0.42 g, 1 mmol) according to a method similar to the method of Example 24-1).

^{1}H-NMR (DMSO-d_6) δ:1.04 (9H, s), 1.25 (6H, d, J = 6.6 Hz), 2.36 (3H, s), 2.90 (2H, s), 3.03-3.13 (1H, m), 3.81 (2H, d, J = 5.4 Hz), 7.22 (2H, d, J = 8.2 Hz), 7.28 (2H, d, J = 8.2 Hz), 8.18 (3H, brs).

Example 63

5-(aminomethyl)-2-isobutyl-4-(4-methylphenyl)-6-neopentylnicotinic acid dihydrochloride

5-(Aminomethyl)-2-isobutyl-4-(4-methylphenyl)-6-neopentylnicotinic acid dihydrochloride (0.41 g, yield 93%) was obtained as a white powder from tert-butyl 5-(aminomethyl)-2-isobutyl-4-(4-methylphenyl)-6-neopentylnicotinate (0.42 g, 1 mmol) according to a method similar to the method of Example 24-1).

^{1}H-NMR (DMSO-d_6) δ:0.89 (6H, d, J = 6.6 Hz), 1.02 (9H, s), 2.18-2.31 (1H, m), 2.37 (3H, s), 2.66 (2H, d, J = 7.2 Hz), 2.91 (2H, s), 3.84 (2H, d,J = 5.1 Hz), 7.21 (2H, d, J = 8.1 Hz), 7.29 (2H, d, J = 8.1 Hz), 8.08 (3H, brs).

Example 64

5-(aminomethyl)-2-benzyl-4-(4-methylphenyl)-6-neopentylnicotinic acid dihydrochloride

5-(Aminomethyl)-2-benzyl-4-(4-methylphenyl)-6-

neopentylnicotinic acid dihydrochloride (0.43 g, yield 91%) was obtained as a white powder from tert-butyl 5-(aminomethyl)-2-benzyl-4-(4-methylphenyl)-6-neopentylnicotinate (0.45 g, 1 mmol) according to a method similar to the method of Example 24-1).

^{1}H-NMR (DMSO-d_6) δ:0.95 (9H, s), 2.37 (3H, s), 2.89 (2H, s), 3.82 (2H, d, J = 5.4 Hz), 4.14 (2H, s), 7.18-7.31 (9H, m), 8.17 (3H, brs).

Example 65

methyl 5-(aminomethyl)-6-butyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) Methyl 6-butyl-5-cyano-2-methyl-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (39 g, yield 24%) was obtained as crystals from 3-oxoheptanenitrile (64 g, 500 mmol) according to a method similar to the method of Example 1-2).

^{1}H-NMR ($CDCl_3$) δ:0.92 (3H, t, J = 7.3 Hz), 1.30-1.42 (2H, m), 1.49-1.60 (2H, m), 2.30 (3H, s), 2.34-2.39 (2H, m), 2.35 (3H, s), 3.58 (3H, s), 4.56 (1H, s), 5.77 (1H, s), 7.07-7.14 (4H, m)

2) Methyl 6-butyl-5-cyano-2-methyl-4-(4-methylphenyl)nicotinate (25 g, yield 65%) was obtained as crystals from methyl 6-butyl-5-cyano-2-methyl-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (25 g, 77 mmol) according to a method similar to the method of Example 1-3).

^{1}H-NMR ($CDCl_3$) δ:0.97 (3H, t, J = 7.3 Hz), 1.40-1.52 (2H, m), 1.74-1.84(2H, m), 2.41 (3H, s), 2.62 (3H, s), 3.04-3.09 (2H, m), 3.60 (3H, s), 7.23-7.29 (4H, m).

3) Methyl 5-(aminomethyl)-6-butyl-2-methyl-4-(4-methylphenyl)nicotinate (17 g, yield 68%) was obtained as an oil from methyl 6-butyl-5-cyano-2-methyl-4-(4-methylphenyl)nicotinate (4 g, 11.9 mmol) according to a method similar to the method of Example 1-4). The oil (3 g) was dissolved in ethyl acetate (10 mL) and 4N hydrogen chloride ethyl acetate solution (10 mL) was added. The mixture was concentrated under reduced pressure to give methyl 5-

(aminomethyl)-6-butyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride as a powder.

^{1}H-NMR (DMSO-d_6) δ:0.95 (3H, t, J = 7.3 Hz), 1.38-1.51 (2H, m), 1.65-1.75 (2H, m), 2.37 (3H, s), 2.53 (3H, s), 2.98-3.03 (2H, m), 3.47 (3H, s), 3.82 (2H, d, J = 5.5 Hz), 7.19 (2H, d, J = 8.1 Hz), 7.30 (2H, d, J = 8.1 Hz), 8.38 (3H, s).

Example 66

5-(aminomethyl)-6-butyl-2-methyl-4-(4-methylphenyl)nicotinic acid dihydrochloride

1) Methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-butyl-2-methyl-4-(4-methylphenyl)nicotinate (16.3 g, yield 89%) was obtained as crystals from methyl 5-(aminomethyl)-6-butyl-2-methyl-4-(4-methylphenyl)nicotinate (14 g, 42.9 mmol) according to a method similar to the method of Example 2-1).

2) 5-{[(tert-Butoxycarbonyl)amino]methyl}-6-butyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.5 g, yield 77%) was obtained as crystals from methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-butyl-2-methyl-4-(4-methylphenyl)nicotinate (2.0 g, 4.7 mmol) according to a method similar to the method of Example 2-2).

3) 5-(Aminomethyl)-6-butyl-2-methyl-4-(4-methylphenyl)nicotinic acid dihydrochloride (0.56 g, yield 86%) was obtained as a white powder from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-butyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.7 g, 1.7 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.95 (3H, t, J = 7.4 Hz), 1.39-1.49 (2H, m), 1.65-1.75 (2H, m), 2.37 (3H, s), 2.61 (3H, s), 3.03-3.08 (2H, m), 3.81 (2H, d, J = 5.3 Hz), 7.24 (2H, d, J = 8.1 Hz), 7.31 (2H, d, J = 8.1 Hz), 8.40 (3H, s).

Example 67

methyl 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-propylnicotinate dihydrochloride

1) Methyl 5-cyano-2-methyl-4-(4-methylphenyl)-6-propyl-1,4-dihydropyridine-3-carboxylate (60 g, yield 39%) was obtained as

an oil from 3-oxohexanenitrile (60 g, 500 mmol) according to a method similar to the method of Example 1-2).

^{1}H-NMR ($CDCl_3$) δ:0.96 (3H, t, J = 7.4 Hz), 1.54-1.66 (2H, m), 2.30 (3H, s), 2.32-2.41 (2H, m), 2.35 (3H, s), 3.58 (3H, s), 4.56 (1H, s), 5.80 (1H, s), 7.09 (2H, d, J = 8.1 Hz), 7.13 (2H, d, J = 8.1 Hz).

2) Methyl 5-cyano-2-methyl-4-(4-methylphenyl)-6-propylnicotinate (34.8 g, yield 58%) was obtained as crystals from methyl 5-cyano-2-methyl-4-(4-methylphenyl)-6-propyl-1,4-dihydropyridine-3-carboxylate (60 g, 193 mmol) according to a method similar to the method of Example 1-3).

^{1}H-NMR ($CDCl_3$) δ:1.05 (3H, t, J = 7.4 Hz), 1.79-1.91 (2H, m), 2.41 (3H, s), 2.62 (3H, s), 3.02-3.07 (2H, m), 3.60 (3H, s), 7.23-7.29 (4H, m).

3) Methyl 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-propylnicotinate (15 g, yield 67%) was obtained as an oil from methyl 5-cyano-2-methyl-4-(4-methylphenyl)-6-propylnicotinate (22 g, 71.3 mmol) according to a method similar to the method of Example 1-4). The oil (2 g) was dissolved in ethyl acetate (10 mL) and 4N hydrogen chloride ethyl acetate solution (10 mL) was added. The mixture was concentrated under reduced pressure to give methyl 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-propylnicotinate dihydrochloride as a powder.

^{1}H-NMR (DMSO-d_6) δ:1.02 (3H, t, J = 7.4 Hz), 1.69-1.82 (2H, m), 2.37 (3H, s), 2.53 (3H, s), 2.96-3.02 (2H, m), 3.47 (3H, s), 3.82 (2H, d, J = 5.5 Hz), 7.19 (2H, d, J = 8.1 Hz), 7.31 (2H, d, J = 8.1 Hz), 8.38 (3H, s).

Example 68

5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-propylnicotinic acid dihydrochloride

1) Methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-propylnicotinate (12 g, yield 70%) was obtained as crystals from methyl 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-propylnicotinate (13 g, 41.6 mmol) according to

a method similar to the method of Example 2-1).

^{1}H-NMR ($CDCl_3$) δ:1.03 (3H, t, J = 7.4 Hz), 1.39 (9H, s), 1.72-1.79 (2H, m), 2.38 (3H, s), 2.53 (3H, s), 2.84-2.90 (2H, m), 3.49 (3H, s), 4.15 (2H, d, J = 5.1 Hz), 4.25 (1H, s), 7.05 (2H, d, J = 8.1 Hz), 7.20 (2H, d, J = 8.1 Hz).

2) 5-{[(tert-Butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-propylnicotinic acid (1.6 g, yield 83%) was obtained as crystals from methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-propylnicotinate (2 g, 4.8 mmol) according to a method similar to the method of Example 2-2).

^{1}H-NMR (DMSO-d_6) δ:0.96 (3H, t, J = 7.4 Hz), 1.35 (9H, s), 1.64-1.76 (2H, m), 2.33 (3H, s), 2.44 (3H, s) 2.67-2.72 (2H, m), 3.87 (2H, d, J = 4.5 Hz), 6.99 (1H, s), 7.16-7.22 (4H, m), 12.92 (1H, s).

3) 5-(Aminomethyl)-2-methyl-4-(4-methylphenyl)-6-propylnicotinic acid dihydrochloride (0.75 g, yield 96%) was obtained as a white powder from 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-propylnicotinic acid (0.7 g, 2.1 mmol) according to a meth d similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:1.02 (3H, t, J = 7.4 Hz), 1.69-1.82 (2H, m), 2.37 (3H, s), 2.62 (3H, s), 3.01-3.07 (2H, m), 3.82 (2H, d, J = 5.3 Hz), 7.24 (2H, d, J = 8.1 Hz), 7.31 (2H, d, J = 8.1 Hz), 8.41 (3H, s).

Example 69

5-(aminomethyl)-4-(4-fluorophenyl)-6-isobutyl-2-methylnicotinic acid dihydrochloride

1) Methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-4-(4-fluorophenyl)-6-isobutyl-2-methylnicotinate (2.60 g, yield 99%) was obtained as a white solid from methyl 5-(aminomethyl)-4-(4-fluorophenyl)-6-isobutyl-2-methylnicotinate (2.00 g, 6.05 mmol) according to a method similar to the method of Example 2-1).

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.16-

2.26 (1H, m), 2.54 (3H, s), 2.78 (2H, d, J = 7.2 Hz), 3.51 (3H, s), 4.08-4.17 (2H, m), 4.22 (1H, brs), 7.07-7.20 (4H, m).

2) 5-{[(tert-Butoxycarbonyl)amino]methyl}-4-(4-fluorophenyl)-6-isobutyl-2-methylnicotinic acid (2.01 g, yield 79%) was obtained as a yellow solid from methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-4-(4-fluorophenyl)-6-isobutyl-2-methylnicotinate (2.60 g, 6.24 mmol) according to a method similar to the method of Example 2-2).

^{1}H-NMR (CD_3OD) δ:1.04 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.12-2.22 (1H, m), 2.71 (3H, s), 2.94 (2H, d, J = 7.4 Hz), 4.13 (2H, s), 7.17-7.25 (2H, m), 7.32-7.39 (2H, m).

3) 5-(Aminomethyl)-4-(4-fluorophenyl)-6-isobutyl-2-methylnicotinic acid dihydrochloride (0.20 g, yield 76%) was obtained as a white solid from 5-{[(tert-butoxycarbonyl)amino]methyl}-4-(4-fluorophenyl)-6-isobutyl-2-methylnicotinic acid (0.28 g, 0.673 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (CD_3OD) δ:1.04-1.13 (6H, m), 2.13-2.28 (1H, m), 2.78-2.86 (3H, m), 3.02-3.11 (2H, m), 4.13-4.20 (2H, m), 7.30-7.38 (2H, m), 7.42-7.51 (2H, m).

Example 70

5-(aminomethyl)-4-(2,6-difluorophenyl)-6-isobutyl-2-methylnicotinic acid dihydrochloride

1) Methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-4-(2,6-difluorophenyl)-6-isobutyl-2-methylnicotinate (2.49 g, yield 87%) was obtained as a white solid from methyl 5-(aminomethyl)-4-(2,6-difluorophenyl)-6-isobutyl-2-methylnicotinate (2.00 g, 6.38 mmol) according to a method similar to the method of Example 2-1).

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.16-2.27 (1H, m), 2.61 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 3.57 (3H, s), 4.13 (2H, d, J = 5.3 Hz), 4.36 (1H, brs), 6.97-7.02 (2H, m), 7.34-7.44 (1H, m).

2) 5-{[(tert-Butoxycarbonyl)amino]methyl}-4-(2,6-

difluorophenyl)-6-isobutyl-2-methylnicotinic acid (2.22 g, yield 92%) was obtained as a yellow solid from methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-4-(2,6-difluorophenyl)-6-isobutyl-2-methylnicotinate (2.49 g, 5.55 mmol) according to a method similar to the method of Example 2-2).

^{1}H-NMR ($CDCl_3$) δ:0.96 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.11-2.26 (1H, m), 2.64 (3H, s), 2.81 (2H, d, J = 7.2 Hz), 4.11-4.16 (2H, m), 4.37 (1H, brs), 6.96-7.01 (2H, m), 7.34-7.43 (1H, m).

3) 5-(Aminomethyl)-4-(2,6-difluorophenyl)-6-isobutyl-2-methylnicotinic acid dihydrochloride (185 mg, yield 70%) was obtained as a white solid from 5-{[(tert-butoxycarbonyl)amino]methyl}-4-(2,6-difluorophenyl)-6-isobutyl-2-methylnicotinic acid (0.28 g, 0.635 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (CD_3OD) δ:1.08 (6H, d, J = 6.8 Hz), 2.19-2.29 (1H, m), 2.81-2.88 (3H, m), 2.98-3.08 (2H, m), 4.09-4.16 (2H, m), 7.20-7.27 (2H, m), 7.64-7.72 (1H, m).

Example 71

tert-butyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-[4-(trifluoromethyl)phenyl]nicotinate

1) 2-(3-Methylbutanoyl)-3-[4-(trifluoromethyl)phenyl]acrylonitrile was obtained as a crude product (9.8 g) from 5-methyl-3-oxohexanenitrile (4.0 g, 32 mmol) and 4-(trifluoromethyl)benzaldehyde (5.6 g, 32 mmol) according to a method similar to the method of Example 29-1).

2) tert-Butyl 5-cyano-6-isobutyl-2-methyl-4-[4-(trifluoromethyl)phenyl]-1,4-dihydropyridine-3-carboxylate (4.8 g, yield 36%) was obtained as a white powder from the crude product (9.8 g) obtained in the aforementioned 1) and tert-butyl 3-aminocrotonate (5.47 g, 35 mmol) according to a method similar to the method of Example 1-2). That is, the aforementioned crude product and tert-butyl 3-aminocrotonate were dissolved in methanol (200 mL) and the mixture was heated under reflux for 1 hr. The reaction mixture was concentrated

under reduced pressure and the residue was purified by silica gel column chromatography to give tert-butyl 5-cyano-6-isobutyl-2-methyl-4-[4-(trifluoromethyl)phenyl]-1,4-dihydropyridine-3-carboxylate.

^{1}H-NMR ($CDCl_3$) δ:0.93 (3H, d, J = 6.6 Hz), 0.99 (3H, d, J = 6.5 Hz), 1.28 (9H, s), 1.75-2.00 (1H, m), 2.10-2.35 (2H, m), 2.36 (3H, s), 4.64 (1H, s), 5.60 (1H, brs), 7.36 (2H, d, J = 8.1 Hz), 7.56 (2H, d, J = 8.1 Hz).

melting point: 199-201°C

3) tert-Butyl 5-cyano-6-isobutyl-2-methyl-4-[4-(trifluoromethyl)phenyl]nicotinate (3.5 g, yield 76%) was obtained as a white powder from tert-butyl 5-cyano-6-isobutyl-2-methyl-4-[4-(trifluoromethyl)phenyl]-1,4-dihydropyridine-3-carboxylate (4.7 g, 11 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:1.02 (6H, d, J = 6.6 Hz), 1.23 (9H, s), 2.20-2.40 (1H, m), 2.67 (3H, s), 2.95 (2H, d, J = 7.4 Hz), 7.51 (2H, d, J = 8.2 Hz), 7.76 (2H, d, J = 8.2 Hz).

melting point: 108-110°C

4) tert-Butyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-[4-(trifluoromethyl)phenyl]nicotinate (3.3 g, yield 96%) was obtained as a white powder from tert-butyl 5-cyano-6-isobutyl-2-methyl-4-[4-(trifluoromethyl)phenyl]nicotinate (3.5 g, 8.2 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.99 (6H, d, J = 6.6 Hz), 1.17 (9H, s), 1.38 (2H, brs), 2.15-2.35 (1H, m), 2.57 (3H, s), 2.80 (2H, d, J = 7.4 Hz), 3.60 (2H, s), 7.42 (2H, d, J = 8.0 Hz), 7.70 (2H, d, J = 8.0 Hz).

melting point: 88-90°C

Example 72

5-(aminomethyl)-6-isobutyl-2-methyl-4-[4-(trifluoromethyl)phenyl]nicotinic acid hydrochloride

5-(Aminomethyl)-6-isobutyl-2-methyl-4-[4-

(trifluoromethyl)phenyl]nicotinic acid hydrochloride (0.51 g, yield 53%) was obtained as a white powder from tert-butyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-[4-(trifluoromethyl)phenyl]nicotinate (1.0 g, 2.3 mmol) according to a method similar to the method of Example 24.

^{1}H-NMR (DMSO-d_6) δ:0.97 (6H, d, J = 6.6 Hz), 2.15-2.35 (1H, m), 2.51 (3H, s), 2.78 (2H, d, J = 7.2 Hz), 3.75 (2H, s), 7.56 (2H, d, J = 8.0 Hz), 7.87 (2H, d, J = 8.0 Hz), 8.01 (2H, brs).

Example 73

tert-butyl 5-(aminomethyl)-6-isobutyl-4-[4-(methoxycarbonyl)phenyl]-2-methylnicotinate

1) Methyl 4-(2-cyano-5-methyl-3-oxohex-1-en-1-yl)benzoate was obtained as a crude product (10.1 g) from 5-methyl-3-oxohexanenitrile (4.0 g, 32 mmol) and methyl 4-formylbenzoate (5.3 g, 32 mmol) according to a method similar to the method of Example 29-1).

2) tert-Butyl 5-cyano-6-isobutyl-4-[4-(methoxycarbonyl)phenyl]-2-methyl-1,4-dihydropyridine-3-carboxylate (5.9 g, yield 45%) was obtained as a white powder from the crude product (10.1 g) obtained in the aforementioned 1) and tert-butyl 3-aminocrotonate (5.25 g, 33 mmol) according to a method similar to the method of Example 1-2). That is, the aforementioned crude product and tert-butyl 3-aminocrotonate were dissolved in methanol (200 mL) and the mixture was heated under reflux for 2 hrs. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give tert-butyl 5-cyano-6-isobutyl-4-[4-(methoxycarbonyl)phenyl]-2-methyl-1,4-dihydropyridine-3-carboxylate.

^{1}H-NMR ($CDCl_3$) δ:0.91 (3H, d, J = 6.6 Hz), 0.98 (3H, d, J = 6.6 Hz), 1.26 (9H, s), 1.75-2.00 (1H, m), 2.15-2.35 (2H, m), 2.36 (3H, s), 3.90 (3H, s), 4.63 (1H, s), 5.69 (1H, brs), 7.32 (2H, d, J = 8.3 Hz), 7.99 (2H, d, J = 8.3 Hz).

melting point: 191-193°C

3) tert-Butyl 5-cyano-6-isobutyl-4-[4-(methoxycarbonyl)phenyl]-2-methylnicotinate (5.4 g, yield 95%) was obtained as a white powder from tert-butyl 5-cyano-6-isobutyl-4-[4-(methoxycarbonyl)phenyl]-2-methyl-1,4-dihydropyridine-3-carboxylate (5.7 g, 14 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:1.01 (6H, d, J = 6.6 Hz), 1.23 (9H, s), 2.20-2.35 (1H, m), 2.67 (3H, s), 2.94 (2H, d, J = 7.4 Hz), 3.96 (3H, s), 7.40-7.50 (2H, m), 8.10-8.20 (2H, m).

melting point: 108-109°C

4) tert-Butyl 5-(aminomethyl)-6-isobutyl-4-[4-(methoxycarbonyl)phenyl]-2-methylnicotinate (5.0 g, yield 94%) was obtained as a white powder from tert-butyl 5-cyano-6-isobutyl-4-[4-(methoxycarbonyl)phenyl]-2-methylnicotinate (5.3 g, 13 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.99 (6H, d, J = 6.6 Hz), 1.17 (9H, s), 1.49 (2H, brs), 2.15-2.35 (1H, m), 2.57 (3H, s), 2.79 (2H, d, J = 7.2 Hz), 3.59 (2H, s), 3.96 (3H, s), 7.30-7.40 (2H, m), 8.05-8.15 (2H, m).

melting point: 77-81°C

Example 74

5-(aminomethyl)-6-isobutyl-4-[4-(methoxycarbonyl)phenyl]-2-methylnicotinic acid hydrochloride

5-(Aminomethyl)-6-isobutyl-4-[4-(methoxycarbonyl)phenyl]-2-methylnicotinic acid hydrochloride (0.50 g, yield 66%) was obtained as a white powder from tert-butyl 5-(aminomethyl)-6-isobutyl-4-[4-(methoxycarbonyl)phenyl]-2-methylnicotinate (0.80 g, 1.9 mmol) according to a method similar to the method of Example 24.

^{1}H-NMR (DMSO-d_6) δ:0.93 (6H, d, J = 6.6 Hz), 2.05-2.25 (1H, m), 2.41 (3H, s), 2.70 (2H, d, J = 7.0 Hz), 3.54 (2H, s), 3.88 (3H, s), 7.41 (2H, d, J = 8.1 Hz), 7.95 (2H, d, J = 8.1 Hz).

Example 75

tert-butyl 5-(aminomethyl)-4-(4-ethylphenyl)-6-isobutyl-2-methylnicotinate

1) 3-(4-Ethylphenyl)-2-(3-methylbutanoyl)acrylonitrile was obtained as a crude product (8.8 g) from 5-methyl-3-oxohexanenitrile (4.0 g, 32 mmol) and 4-ethylbenzaldehyde (4.3 g, 32 mmol) according to a method similar to the method of Example 29-1).

2) tert-Butyl 5-cyano-4-(4-ethylphenyl)-6-isobutyl-2-methyl-1,4-dihydropyridine-3-carboxylate (7.8 g, yield 64%) was obtained as a white powder from the crude product (8.8 g) obtained in the aforementioned 1) and tert-butyl 3-aminocrotonate (5.47 g, 35 mmol) according to a method similar to the method of Example 1-2). That is, the aforementioned crude product and tert-butyl 3-aminocrotonate were dissolved in methanol (200 mL) and the mixture was heated under reflux for 4 hrs. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give tert-butyl 5-cyano-4-(4-ethylphenyl)-6-isobutyl-2-methyl-1,4-dihydropyridine-3-carboxylate.

^{1}H-NMR ($CDCl_3$) δ:0.94 (3H, d, J = 6.5 Hz), 0.99 (3H, d, J = 6.5 Hz), 1.20 (3H, t, J = 7.6 Hz), 1.28 (9H, s), 1.80-2.00 (1H, m), 2.10-2.30 (2H, m), 2.32 (3H, s), 2.61 (2H, q, J = 7.6 Hz), 4.52 (1H, s), 5.55 (1H, brs), 7.10 (2H, d, J = 8.3 Hz), 7.14 (2H, d, J = 8.3 Hz).

melting point: 165-166°C

3) tert-Butyl 5-cyano-4-(4-ethylphenyl)-6-isobutyl-2-methylnicotinate (5.2 g, yield 67%) was obtained as a white powder from tert-butyl 5-cyano-4-(4-ethylphenyl)-6-isobutyl-2-methyl-1,4-dihydropyridine-3-carboxylate (7.8 g, 21 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:1.01 (6H, d, J = 6.6 Hz), 1.23 (9H, s), 1.26 (3H, t, J = 7.6 Hz), 2.20-2.35 (1H, m), 2.64 (3H, s), 2.71 (2H, q, J = 7.6 Hz), 2.94 (2H, d, J = 7.4 Hz), 7.20-7.35 (4H, m).

melting point: 85-86°C

4) tert-Butyl 5-(aminomethyl)-4-(4-ethylphenyl)-6-isobutyl-2-methylnicotinate (7.0 g, yield 97%) was obtained as a white powder from tert-butyl 5-cyano-4-(4-ethylphenyl)-6-isobutyl-2-methylnicotinate (7.2 g, 19 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.6 Hz), 1.17 (9H, s), 1.25 (3H, t, J = 7.5 Hz), 1.38 (2H, brs), 2.15-2.30 (1H, m), 2.55 (3H, s), 2.69 (2H, q, J = 7.5 Hz), 2.78 (2H, d, J = 7.4 Hz), 3.63 (2H, s), 7.15 (2H, d, J = 7.9 Hz), 7.24 (2H, d, J = 7.9 Hz).

melting point: 50-52°C

Example 76

5-(aminomethyl)-4-(4-ethylphenyl)-6-isobutyl-2-methylnicotinic acid hydrochloride

5-(Aminomethyl)-4-(4-ethylphenyl)-6-isobutyl-2-methylnicotinic acid hydrochloride (0.52 g, yield 79%) was obtained as a white powder from tert-butyl 5-(aminomethyl)-4-(4-ethylphenyl)-6-isobutyl-2-methylnicotinate (0.70 g, 1.8 mmol) according to a method similar to the method of Example 24.

^{1}H-NMR (DMSO-d_6) δ:0.95 (6H, d, J = 7.5 Hz), 1.23 (3H, t, J = 7.5 Hz), 2.10-2.30 (1H, m), 2.47 (3H, s), 2.67 (2H, q, J = 7.5 Hz), 2.77 (2H, d, J = 7.0 Hz), 3.74 (2H, s), 7.22 (2H, d, J = 8.0 Hz), 7.30 (2H, d, J = 8.0 Hz), 8.81 (1H, brs).

Example 77

methyl 5-(aminomethyl)-4-(4-chlorophenyl)-2-ethyl-6-neopentylnicotinate

1) Methyl 3-aminopent-2-enoate was obtained as a crude product (20 g) from methyl 3-oxopentanoate (13 g, 100 mmol) and ammonium acetate (38.5 g, 500 mmol) according to a method similar to the method of Example 12-1).

2) Methyl 4-(4-chlorophenyl)-5-cyano-2-ethyl-6-neopentyl-1,4-dihydropyridine-3-carboxylate (1.4 g, yield 23%) was obtained as a yellow powder from 5,5-dimethyl-3-oxohexanenitrile (5.1 g,

32 mmol), 4-chlorobenzaldehyde (4.5 g, 32 mmol) and the crude product (3.2 g) obtained in the aforementioned 1), according to a method similar to the meth d of Example 1-2).

^{1}H-NMR ($CDCl_3$) δ:0.95-1.05 (3H, m), 1.01 (9H, s), 2.20 (1H, d, J = 13.8 Hz), 2.37 (1H, d, J = 13.8 Hz), 2.77 (2H, q, J = 7.5 Hz), 3.58 (3H, s), 4.60 (1H, s), 5.63 (1H, brs), 7.10-7.20 (2H, m), 7.25-7.30 (2H, m).

3) Methyl 4-(4-chlorophenyl)-5-cyano-2-ethyl-6-neopentylnicotinate (0.58 g, yield 43%) was obtained as a pale-yellow powder from methyl 4-(4-chlorophenyl)-5-cyano-2-ethyl-6-neopentyl-1,4-dihydropyridine-3-carboxylate (1.4 g, 3.7 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:1.07 (9H, s), 1.33 (3H, t, J = 7.5 Hz), 2.87 (2H, q, J = 7.5 Hz), 3.03 (2H, s), 3.61 (3H, s), 7.25-7.35 (2H, m), 7.45-7.50 (2H, m).

melting point: 120-121°C

4) Methyl 5-(aminomethyl)-4-(4-chlorophenyl)-2-ethyl-6-neopentylnicotinate (0.49 g, yield 85%) was obtained as a pale-yellow oil from methyl 4-(4-chlorophenyl)-5-cyano-2-ethyl-6-neopentylnicotinate (0.57 g, 1.5 mmol) according to a method similar to the method of Example 23-4).

^{1}H-NMR ($CDCl_3$) δ:1.03 (9H, s), 1.30 (3H, t, J = 7.5 Hz), 1.42 (2H, brs), 2.77 (2H, q, J = 7.5 Hz), 2.89 (2H, s), 3.51 (3H, s), 3.69 (2H, s), 7.15-7.25 (2H, m), 7.35-7.45 (2H, m).

Example 78

5-(aminomethyl)-4-(4-chlorophenyl)-2-ethyl-6-neopentylnicotinic acid dihydrochloride

1) Methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-4-(4-chlorophenyl)-2-ethyl-6-neopentylnicotinate (0.52 g, yield 97%) was obtained as a white powder from methyl 5-(aminomethyl)-4-(4-chlorophenyl)-2-ethyl-6-neopentylnicotinate (0.42 g, 1.1 mmol) according to a method similar to the method of Example 2-1).

^{1}H-NMR ($CDCl_3$) δ:1.02 (9H, s), 1.30 (3H, t, J = 7.5 Hz), 1.38

(9H, s), 2.78 (2H, q, J = 7.5 Hz), 2.87 (2H, s), 3.51 (3H, s), 4.18 (3H, brs), 7.10-7.20 (2H, m), 7.30-7.45 (2H, m).

2) 5-{[(tert-Butoxycarbonyl)amino]methyl}-4-(4-chlorophenyl)-2-ethyl-6-neopentylnicotinic acid (0.37 g, yield 81%) was obtained as a white powder from methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-4-(4-chlorophenyl)-2-ethyl-6-neopentylnicotinate (0.47 g, 0.99 mmol) according to a method similar to the method of Example 2-2).

^{1}H-NMR ($CDCl_3$) δ:1.01 (9H, s), 1.24 (3H, t, J = 7.4 Hz), 1.33 (9H, s), 2.73 (2H, q, J = 7.4 Hz), 2.73 (2H, s), 3.92 (2H, d, J = 4.5 Hz), 6.96 (1H, t, J = 4.5 Hz), 7.25-7.35 (2H, m), 7.47 (2H, d, J = 8.3 Hz), 13.05 (1H, brs).

melting point: 71-72°C

3) 5-(Aminomethyl)-4-(4-chlorophenyl)-2-ethyl-6-neopentylnicotinic acid dihydrochloride (0.24 g, yield 83%) was obtained as a white powder from 5-{[(tert-butoxycarbonyl)amino]methyl}-4-(4-chlorophenyl)-2-ethyl-6-neopentylnicotinic acid (0.30 g, 0.65 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:1.03 (9H, s), 1.26 (3H, t, J = 7.4 Hz), 2.79 (2H, q, J = 7.4 Hz), 2.90 (2H, brs), 3.83 (2H, d, J = 5.7 Hz), 7.36 (2H, d, J = 8.5 Hz), 7.50-7.60 (2H, m), 8.12 (3H, brs).

melting point: 230-235°C

Example 79

tert-butyl 5-(aminomethyl)-4-(4-chlorophenyl)-2-isopropyl-6-neopentylnicotinate

1) tert-Butyl 4-(4-chlorophenyl)-5-cyano-2-isopropyl-6-neopentyl-1,4-dihydropyridine-3-carboxylate (2.00 g, yield 16%) was obtained as a white solid from 5,5-dimethyl-3-oxohexanenitrile (5.67 g, 36.7 mmol), 4-chlorobenzaldehyde (5.16 g, 36.7 mmol) and tert-butyl 3-amino-4-methylpent-2-enoate (5.98 g, 30 mmol) according to a method similar to the method f Example 1-2).

^{1}H-NMR ($CDCl_3$) δ:1.02 (9H, s), 1.04 (3H, d, J = 6.8 Hz), 1.21

(3H, d, J = 7.0 Hz), 1.28 (9H, s), 2.20 (1H, d, J = 13.9 Hz), 2.33 (1H, d, J = 14.1 Hz), 4.07-4.30 (1H, m), 4.55 (1H, s), 5.65 (1H, s), 7.16 (2H, d, J = 8.3 Hz), 7.22-7.35 (2H, m).

2) tert-Butyl 4-(4-chlorophenyl)-5-cyano-2-isopropyl-6-neopentylnicotinate (1.91 g, yield 96%) was obtained as a yellow solid from tert-butyl 4-(4-chlorophenyl)-5-cyano-2-isopropyl-6-neopentyl-1,4-dihydropyridine-3-carboxylate (2.00 g, 4.66 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:1.06 (9H, s), 1.27 (9H, s), 1.32 (6H, d, J = 6.6 Hz), 3.00 (2H, s), 3.13-3.25 (1H, m), 7.32 (2H, d, J = 8.5 Hz), 7.45 (2H, d, J = 8.5 Hz).

3) tert-Butyl 5-(aminomethyl)-4-(4-chlorophenyl)-2-isopropyl-6-neopentylnicotinate (1.24 g, yield 67%) was obtained as a white solid from tert-butyl 4-(4-chlorophenyl)-5-cyano-2-isopropyl-6-neopentylnicotinate (1.80 g, 4.27 mmol) according to a method similar to the method of Example 23-4).

^{1}H-NMR ($CDCl_3$) δ:1.04 (9H, s), 1.21 (9H, s), 1.30 (6H, d, J = 6.6 Hz), 2.85 (2H, s), 3.01-3.16 (1H, m), 3.64 (2H, s), 7.22 (2H, d, J = 8.5 Hz), 7.40 (2H, d, J = 8.5 Hz).

Example 80

5-(aminomethyl)-4-(4-chlorophenyl)-2-isopropyl-6-neopentylnicotinic acid dihydrochloride

5-(Aminomethyl)-4-(4-chlorophenyl)-2-isopropyl-6-neopentylnicotinic acid dihydrochloride (393 mg, yield 93%) was obtained as a yellow solid from tert-butyl 5-(aminomethyl)-4-(4-chlorophenyl)-2-isopropyl-6-neopentylnicotinate (406 mg, 0.941 mmol) according to a method similar to the method of Example 24-1).

^{1}H-NMR (DMSO-d_6) δ:1.04 (9H, s), 1.25 (6H, d, J = 6.8 Hz), 2.88 (2H, s), 3.05-3.14 (1H, m), 3.81 (2H, d, J = 5.3 Hz), 7.36 (2H, d, J = 8.5 Hz), 7.55 (2H, d, J = 8.5 Hz), 8.11 (3H, brs).

Example 81

tert-butyl 5-(aminomethyl)-4-(4-chlorophenyl)-6-isobutyl-2-

isopropylnicotinate

1) tert-Butyl 4-(4-chlorophenyl)-5-cyano-6-isobutyl-2-isopropyl-1,4-dihydropyridine-3-carboxylate (6.18 g, yield 50%) was obtained as a yellow solid from 5-methyl-3-oxohexanenitrile (4.14 g, 33 mmol), 4-chlorobenzaldehyde (4.64 g, 33 mmol) and tert-butyl 3-amino-4-methylpent-2-enoate (5.98 g, 30 mmol) according to a method similar to the method of Example 1-2).

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, dd, J = 8.5, 6.8 Hz), 1.14 (3H, d, J = 7.0 Hz), 1.22 (3H, d, J = 7.0 Hz), 1.28 (9H, s), 1.81-1.98 (1H, m), 2.25 (2H, d, J = 7.4 Hz), 4.09-4.26 (1H, m), 4.55 (1H, s), 5.71 (1H, s), 7.15 (2H, d, J = 8.3 Hz), 7.25-7.27 (2H, m).

2) tert-Butyl 4-(4-chlorophenyl)-5-cyano-6-isobutyl-2-isopropylnicotinate (6.10 g, yield 99%) was obtained as a yellow oil from tert-butyl 4-(4-chlorophenyl)-5-cyano-6-isobutyl-2-isopropyl-1,4-dihydropyridine-3-carboxylate (6.16 g, 14.8 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:1.01 (6H, d, J = 6.6 Hz), 1.26 (9H, s), 1.32 (6H, d, J = 6.8 Hz), 2.22-2.39 (1H, m), 2.95 (2H, d, J = 7.2 Hz), 3.19-3.25 (1H, m), 7.33 (2H, d, J = 8.7 Hz), 7.46 (2H, d, J = 8.7 Hz).

3) tert-Butyl 5-(aminomethyl)-4-(4-chlorophenyl)-6-isobutyl-2-isopropylnicotinate (5.52 g, yield 89%) was obtained as a white solid from tert-butyl 4-(4-chlorophenyl)-5-cyano-6-isobutyl-2-isopropylnicotinate (6.10 g, 1.48 mmol) according to a method similar to the method of Example 23-4).

^{1}H-NMR ($CDCl_3$) δ:0.99 (6H, d, J = 6.8 Hz), 1.21 (9H, s), 1.30 (6H, d, J = 6.8 Hz), 2.23-2.39 (1H, m), 2.78 (2H, d, J = 7.2 Hz), 3.01-3.16 (1H, m), 3.59 (1H, s), 7.22 (2H, d, J = 8.5 Hz), 7.39 (2H, d, J = 8.5 Hz).

Example 82

5-(aminomethyl)-4-(4-chlorophenyl)-6-isobutyl-2-isopropylnicotinic acid dihydrochloride

5-(Aminomethyl)-4-(4-chlorophenyl)-6-isobutyl-2-

isopropylnicotinic acid dihydrochloride (263 mg, yield 62%) was obtained as a yellow solid from tert-butyl 5-(aminomethyl)-4-(4-chlorophenyl)-6-isobutyl-2-isopropylnicotinate (404 mg, 0.969 mmol) according to a method similar to the method of Example 24-1).

^{1}H-NMR (DMSO-d_6) δ:0.99 (6H, d, J = 6.6 Hz), 1.25 (6H, d, J = 6.8 Hz), 2.20-2.39 (1H, m), 2.83 (2H, d, J = 7.0 Hz), 3.01-3.19 (1H, m), 3.77 (2H, d, J = 5.3 Hz), 7.36 (2H, d, 8.5 Hz), 7.55 (2H, d, J = 8.3 Hz), 8.14 (3H, brs).

Example 83

tert-butyl 5-(aminomethyl)-4-(4-chlorophenyl)-2,6-diisobutylnicotinate

1) tert-Butyl 3-amino-5-methylhex-2-enoate was obtained as a crude product (20.2 g) from Meldrum's acid (17.3 g, 120 mmol) and isovaleryl chloride (15.8 mL, 132 mmol) according to a method similar to the method of Example 25-1).

2) tert-Butyl 4-(4-chlorophenyl)-5-cyano-2,6-diisobutyl-1,4-dihydropyridine-3-carboxylate (10.2 g, yield 72%) was obtained as a pale-yellow powder from 5-methyl-3-oxohexanenitrile (4.1 g, 33 mmol), 4-chlorobenzaldehyde (4.6 g, 33 mmol) and the crude product (10.1 g) obtained in the aforementioned 1), according to a method similar to the method of Example 1-2).

^{1}H-NMR ($CDCl_3$) δ:0.95-1.05 (12H, m), 1.29 (9H, s), 1.80-2.05 (2H, m), 2.15-2.35 (2H, m), 2.55-2.70 (2H, m), 4.60 (1H, s), 5.51 (1H, brs), 7.15-7.25 (2H, m), 7.25-7.30 (2H, m).

melting point: 166-168°C

3) tert-Butyl 4-(4-chlorophenyl)-5-cyano-2,6-diisobutylnicotinate (9.6 g, yield 99%) was obtained as a white powder from tert-butyl 4-(4-chlorophenyl)-5-cyano-2,6-diisobutyl-1,4-dihydropyridine-3-carboxylate (9.8 g, 23 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:0.95 (6H, d, J = 6.8 Hz), 1.00 (6H, d, J = 6.6 Hz), 1.25 (9H, s), 2.15-2.40 (2H, m), 2.76 (2H, d, J = 7.2 Hz), 2.95 (2H, d, J = 7.4 Hz), 7.30-7.35 (2H, m), 7.40-7.50 (2H, m).

4) tert-Butyl 5-(aminomethyl)-4-(4-chlorophenyl)-2,6-diisobutylnicotinate (0.97 g, yield 96%) was obtained as a white powder from tert-butyl 4-(4-chlorophenyl)-5-cyano-2,6-diisobutylnicotinate (1.0 g, 2.3 mmol) according to a method similar to the method of Example 23-4).

^{1}H-NMR ($CDCl_3$) δ:0.94 (6H, d, J = 6.6 Hz), 0.98 (6H, d, J = 6.6 Hz), 1.20 (9H, s), 1.48 (2H, brs), 2.15-2.35 (2H, m), 2.67 (2H, d, J = 7.4 Hz), 2.80 (2H, d, J = 7.4 Hz), 3.61 (2H, s), 7.20-7.25 (2H, m), 7.35-7.45 (2H, m).

Example 84

5-(aminomethyl)-4-(4-chlorophenyl)-2,6-diisobutylnicotinic acid dihydrochloride

5-(Aminomethyl)-4-(4-chlorophenyl)-2,6-diisobutylnicotinic acid dihydrochloride (0.92 g, yield 98%) was obtained as a white powder from tert-butyl 5-(aminomethyl)-4-(4-chlorophenyl)-2,6-diisobutylnicotinate (0.90 g, 2.1 mmol) according to a method similar to the method of Example 24-1).

^{1}H-NMR (DMSO-d_6) δ:0.90 (6H, d, J = 6.6 Hz), 0.97 (6H, d, J = 6.6 Hz), 2.10-2.35 (2H, m), 2.66 (2H, d, J = 6.4 Hz), 2.84 (2H, d, J = 6.2 Hz), 3.79 (2H, d, J = 5.5 Hz), 7.36 (2H, d, J = 8.5 Hz), 7.50-7.60 (2H, m), 8.17 (3H, brs).

melting point: 205°C (dec.)

Example 85

tert-butyl 5-(aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-6-neopentylnicotinate

1) tert-Butyl 4-(4-chlorophenyl)-5-cyano-2-isobutyl-6-neopentyl-1,4-dihydropyridine-3-carboxylate was obtained as a crude product (7.9 g) from 5,5-dimethyl-3-oxohexanenitrile (4.6 g, 33 mmol), 4-chlorobenzaldehyde (4.6 g, 33 mmol) and the crude product (10.1 g) of tert-butyl 3-amino-5-methylhex-2-enoate obtained in Example 83-1), according to a method similar to the method of Example 1-2).

2) tert-Butyl 4-(4-chlorophenyl)-5-cyano-2-isobutyl-6-neopentylnicotinate (5.5 g, yield 37%) was obtained as a white

powder from the crude product (7.9 g) obtained in the aforementioned 1) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:0.95 (6H, d, J = 6.6 Hz), 1.06 (9H, s), 1.26 (9H, s), 2.20-2.35 (1H, m), 2.76 (2H, d, J = 7.2 Hz), 3.01 (2H, s), 7.30-7.35 (2H, m), 7.40-7.50 (2H, m).

3) tert-Butyl 5-(aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-6-neopentylnicotinate (4.5 g, yield 86%) was obtained as a yellow powder from tert-butyl 4-(4-chlorophenyl)-5-cyano-2-isobutyl-6-neopentylnicotinate (5.2 g, 12 mmol) according to a method similar to the method of Example 23-4).

^{1}H-NMR ($CDCl_3$) δ:0.93 (6H, d, J = 6.8 Hz), 1.02 (9H, s), 1.20 (9H, s), 1.86 (2H, brs), 2.15-2.35 (1H, m), 2.67 (2H, d, J = 7.4 Hz), 2.87 (2H, s), 3.71 (2H, s), 7.20-7.25 (2H, m), 7.35-7.45 (2H, m).

Example 86

5-(aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-6-neopentylnicotinic acid dihydrochloride

5-(Aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-6-neopentylnicotinic acid dihydrochloride (0.29 g, yield 56%) was obtained as a white powder from tert-butyl 5-(aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-6-neopentylnicotinate (0.50 g, 1.1 mmol) according to a method similar to the method of Example 24-1).

^{1}H-NMR (DMSO-d_6) δ:0.90 (6H, d, J = 6.6 Hz), 1.02 (9H, s), 2.15-2.30 (1H, m), 2.66 (2H, q, J = 7.2 Hz), 2.91 (2H, s), 3.84 (2H, d, J = 5.5 Hz), 7.30-7.40 (2H, m), 7.50-7.60 (2H, m), 8.12 (3H, brs).

melting point: 251°C (dec.)

Example 87

[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetonitrile dihydrochloride

1) tert-Butyl {[5-(hydroxymethyl)-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (4.5 g, yield 48%) was

obtained as a white powder from methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate (10 g, 22.7 mmol) according to a method similar to the method of Example 5-1).

^{1}H-NMR ($CDCl_3$) δ:1.01 (9H, s), 1.37 (9H, s), 2.41 (3H, s), 2.67 (3H, s), 2.84 (2H, s), 4.10 (2H, d, J = 4.9 Hz), 4.16 (1H, s), 4.36 (2H, d, J = 5.7 Hz), 7.05 (2H, d, J = 8.1 Hz), 7.26 (2H, d, J = 8.1 Hz).

2) A mixture of tert-butyl {[5-(hydroxymethyl)-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (0.9 g, 2.2 mmol), triethylamine (0.4 g, 4.0 mmol) and tetrahydrofuran (30 mL) was cooled to 0°C and methanesulfonyl chloride (0.3 g, 2.6 mmol) was added dropwise. After stirring at room temperature for 30 min., the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the extract was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give [5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl methanesulfonate (0.85 g, yield 79%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:1.01 (9H, s), 1.37 (9H, s), 2.41 (3H, s), 2.67 (3H, s), 2.75 (3H, s), 2.86 (2H, s), 4.11 (2H, d, J = 4.9 Hz), 4.17 (1H, s), 4.91 (2H, s), 7.04 (2H, d, J = 8.1 Hz), 7.27 (2H, d, J = 8.1 Hz).

3) [5-{[(tert-Butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl methanesulfonate (0.84 g, 1.7 mmol) was dissolved in dimethyl sulfoxide (10 mL) and potassium cyanide (0.14 g, 2.0 mmol) was added. The mixture was stirred at 60°C for 1 hr. Ethyl acetate was added to the reaction mixture, and the mixture was washed successively with water and saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel

column chromatography to give tert-butyl {[5-(cyanomethyl)-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (0.45 g, yield 63%) as a powder.

^{1}H-NMR ($CDCl_3$) δ:1.01 (9H, s), 1.37 (9H, s), 2.43 (3H, s), 2.65 (3H, s), 2.85 (2H, s), 3.30 (2H, s), 4.11 (2H, d, J = 4.5 Hz), 4.17 (1H, s), 7.05 (2H, d, J = 8.0 Hz), 7.30 (2H, d, J = 8.0 Hz).

4) [5-(Aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetonitrile dihydrochloride (0.28 g, 76%) was obtained as a powder from tert-butyl {[5-(cyanomethyl)-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (0.4 g, 0.95 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:1.01 (9H, s), 2.42 (3H, s), 2.76 (3H, s), 3.06 (2H, s), 3.59 (2H, s), 3.80 (2H, d, J = 5.3 Hz), 7.24 (2H, d, J = 7.9 Hz), 7.42 (2H, d, J = 7.9 Hz), 8.20 (3H, s).

Example 88

2-[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetamide dihydrochloride

1) tert-Butyl {[5-(2-amino-2-oxoethyl)-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (0.3 g, 82%) was obtained as a powder from tert-butyl {[5-(cyanomethyl)-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (0.35 g, 0.83 mmol) according to a method similar to the method of Example 6-1).

^{1}H-NMR ($CDCl_3$) δ:1.02 (9H, s), 1.37 (9H, s), 2.40 (3H, s), 2.56 (3H, s), 2.84 (2H, s), 3.30 (2H, s), 4.10 (2H, d, J = 4.9 Hz), 4.19 (1H, s), 5.15 (1H, s), 5.20 (1H, s), 7.00 (2H, d, J = 7.9 Hz), 7.24 (2H, d, J = 7.9 Hz).

2) 2-[5-(Aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetamide dihydrochloride (0.18 g, 85%) was obtained as a powder from tert-butyl {[5-(2-amino-2-oxoethyl)-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (0.22 g, 0.5 mmol) according to a method

similar to the method of Example 6-2).

^{1}H-NMR (DMSO-d_6) δ:1.03 (9H, s), 2.41 (3H, s), 2.77 (2H, s), 3.29 (3H, s), 3.87 (2H, s), 4.28 (2H, s), 7.03 (1H, s), 7.20 (2H, d, J = 7.8 Hz), 7.38 (2H, d, J = 7.8 Hz), 7.39 (1H, s), 8.24 (3H, s).

Example 89

[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl acetate dihydrochloride

1) A mixture of tert-butyl {[5-(hydroxymethyl)-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (0.3 g, 0.73 mmol), triethylamine (0.1 g, 1.0 mmol) and tetrahydrofuran (20 mL) was cooled to 0°C and acetyl chloride (0.06 g, 0.8 mmol) was added dropwise. After stirring at room temperature for 30 min., the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the extract was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give [5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl acetate (0.26 g, yield 76%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:1.02 (9H, s), 1.37 (9H, s), 2.00 (3H, s), 2.40 (3H, s), 2.57 (3H, s), 2.85 (2H, s), 4.11 (2H, d, J=4.9 Hz), 4.17 (1H, s), 4.76 (2H, s), 7.00 (2H, d, J = 8.1 Hz), 7.22 (2H, d, J = 8.1 Hz).

2) [5-(Aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl acetate dihydrochloride (99 mg, 90%) was obtained as a powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl acetate (0.12 g, 0.26 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:1.02 (9H, s), 1.96 (3H, s), 2.40 (3H, s), 2.78 (3H, s), 3.14 (2H, s), 3.82 (2H, s), 4.72 (2H, s), 7.21 (2H, d, J = 7.8 Hz), 7.36 (2H, d, J = 7.8 Hz), 8.23 (3H, s).

Example 90

{[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-({[4-(methylthio)phenyl]thio}methyl)pyridin-3-yl]methyl}amine dihydrochloride

1) A mixture of tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (3.06 g, 7.68 mmol), triethylamine (1.8 mL, 12.9 mmol) and tetrahydrofuran (30 mL) was cooled to 0°C, and methanesulfonyl chloride (0.89 mL, 11.5 mmol) was added dropwise. After stirring at room temperature for 30 min., the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to give [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl methanesulfonate as a crude product. The crude product was dissolved in N,N-dimethylformamide (30 mL). Potassium carbonate (1.77 g, 12.8 mmol) and 4-(methylthio)benzenethiol (1.00 g, 6.40 mmol) were added and the mixture was stirred with heating at 50°C for 1 hr. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give tert-butyl {[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-({[4-(methylthio)phenyl]thio}methyl)pyridin-3-yl]methyl}carbamate (3.43 g, yield 99%) as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.15-2.24 (1H, m), 2.40 (3H, s), 2.45 (3H, s), 2.63 (3H, s), 2.75 (2H, d, J = 7.4 Hz), 3.75 (2H, s), 4.02 (2H, d, J = 5.1 Hz), 4.18 (1H, brs), 6.98 (2H, d, J = 8.1 Hz), 7.03 (2H, d, J = 8.7 Hz), 7.08 (2H, d, J = 8.7 Hz), 7.20 (2H, d, J = 7.9 Hz).

2) {[2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-({[4-(methylthio)phenyl]thio}methyl)pyridin-3-yl]methyl}amine

dihydrochloride (380 mg, yield 79%) was obtained as a yellow solid from tert-butyl {[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-({[4-(methylthio)phenyl]thio}methyl)pyridin-3-yl]methyl}carbamate (508 mg, 0.947 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.98 (6H, d, J = 6.6 Hz), 2.13-2.22 (1H, m), 2.40 (3H, s), 2.46 (3H, s), 2.78 (3H, s), 3.11 (2H, brs), 3.76 (2H, d, J = 4.5 Hz), 3.87 (2H, s), 7.12 (2H, d, J = 8.7 Hz), 7.16 (2H, d, J = 8.7 Hz), 7.22 (2H, d, J = 7.9 Hz), 7.33 (2H, d, J = 7.9 Hz), 8.38 (3H, brs).

Example 91

{[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-({[4-(methylsulfonyl)phenyl]sulfonyl}methyl)pyridin-3-yl]methyl}amine dihydrochloride

1) To a solution of tert-butyl {[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-({[4-(methylthio)phenyl]thio}methyl)pyridin-3-yl]methyl}carbamate (1.10 g, 2.05 mmol) in methanol (15 mL), water (1.5 mL) and tetrahydrofuran (1.5 mL) were added sulfuric acid (121 mg, 1.23 mmol) and Oxone (trademark, 3.78 g, 6.15 mmol) and the mixture was stirred at room temperature for 2 hrs. The reaction mixture was diluted with ethyl acetate (100 mL) and washed successively with saturated aqueous sodium hydrogen carbonate and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained white solid was washed with diisopropyl ether to give tert-butyl {[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-({[4-(methylsulfonyl)phenyl]sulfonyl}methyl)pyridin-3-yl]methyl}carbamate (1.06 g, yield 86%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.8 Hz), 1.38 (9H, s), 2.17-2.27 (1H, m), 2.42 (3H, s), 2.70 (3H, s), 2.78 (2H, d, J = 7.2 Hz), 3.09 (3H, s), 4.00 (2H, d, J = 5.1 Hz), 4.19 (1H, brs), 4.36 (2H, s), 6.87 (2H, d, J = 7.9 Hz), 7.19 (2H, d, J = 7.9 Hz), 7.69 (2H, d, J = 8.3 Hz), 8.00 (2H, d, J = 8.5 Hz).

2) {[2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-({[4-(methylsulfonyl)phenyl]sulfonyl}methyl)pyridin-3-yl]methyl}amine dihydrochloride (480 mg, yield 98%) was obtained as a white powder from tert-butyl {[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-({[4-(methylsulfonyl)phenyl]sulfonyl}methyl)pyridin-3-yl]methyl}carbamate (511 mg, 0.851 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.97 (6H, d, J = 6.6 Hz), 2.17-2.27 (1H, m), 2.38 (3H, s), 2.81 (3H, brs), 3.00 (2H, brs), 3.34 (3H, s), 3.68 (2H, brs), 7.03 (2H, d, J = 7.4 Hz), 7.22 (2H, d, J = 7.9 Hz), 7.77 (2H, d, J = 7.0 Hz), 8.11 (2H, d, J = 8.5 Hz), 8.26 (3H, brs).

Example 92

(6-methyl-4-(4-methylphenyl)-5-{[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl}-2-neopentylpyridin-3-yl)methylamine dihydrochloride

1) tert-Butyl [(6-methyl-4-(4-methylphenyl)-5-{[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl}-2-neopentylpyridin-3-yl)methyl]carbamate (0.28 g, 77%) was obtained as a powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl methanesulfonate (0.35 g, 0.71 mmol) and 4-methyl-4H-1,2,4-triazole-3-thiol (99 mg, 0.86 mmol) according to a method similar to the method of Example 33-1).

^{1}H-NMR ($CDCl_3$) δ:1.02 (9H, s), 1.37 (9H, s), 2.39 (3H, s), 2.65 (3H, s), 2.84 (2H, s), 3.41 (3H, s), 4.07 (2H, d, J = 5.3 Hz), 4.17 (3H, s), 7.02 (2H, d, J = 7.9 Hz), 7.22 (2H, d, J = 7.9 Hz), 8.08 (1H, s).

2) (6-Methyl-4-(4-methylphenyl)-5-{[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl}-2-neopentylpyridin-3-yl)methylamine dihydrochloride (0.12 g, 72%) was obtained as a powder from tert-butyl [(6-methyl-4-(4-methylphenyl)-5-{[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl}-2-neopentylpyridin-3-

min. and water was added to the reaction mixture. The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in toluene (3 mL). The mixture was heated under reflux with stirring for 1 hr. 25% Aqueous ammonia (3 mL) was added to the reaction mixture and the mixture was stirred at 100°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. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give tert-butyl {[5-[(aminocarbonyl)amino]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (101 mg, yield 24%) as white crystals.

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.15-2.26 (1H, m), 2.39 (3H, s), 2.56 (3H, s), 2.76 (2H, d, J = 7.2 Hz), 4.10 (2H, d, J = 5.1 Hz), 4.24 (1H, brs), 4.38 (2H, s), 5.50 (1H, s), 7.01 (2H, d, J = 7.5 Hz), 7.24 (2H, d, J = 7.5 Hz).

2) N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]urea dihydrochloride (84 mg, yield 92%) was obtained as a white powder from tert-butyl {[5-[(aminocarbonyl)amino]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (100 mg, 0.23 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.98 (6H, d, J = 5.4 Hz), 2.14-2.19 (1H, m), 2.40 (3H, s), 2.53 (3H, s), 3.0. (2H, brs), 3.80 (2H, brs), 3.83 (1H, brs), 5.94 (1H, brs), 7.20 (2H, d, J = 7.8Hz), 7.36 (2H, d, J = 7.8 Hz), 8.28 (3H, brs).

Example 96

N'-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N,N-dimethylurea dihydrochloride

isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1750 mg, 4.2 mmol) in dichloromethane was added triethylamine (1.2 mL, 8.4 mmol), and trifluoromethanesulfonic anhydride (780 μL, 8.4 mmol) was added dropwise under ice-cooling. The mixture was stirred for 30 min. and the reaction mixture was washed successively with water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give tert-butyl {[5-cyano-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1130 mg, yield 68%) as white crystals.

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.40 (9H, s), 2.20-2.29 (1H, m), 2.43 (3H, s), 2.77 (3H, s), 2.83 (2H, d, J = 9.0 Hz), 4.18 (2H, s), 4.20 (1H, brs), 7.13 (2H, d, J = 6.0 Hz), 7.31 (2H, d, J = 6.0 Hz).

2) 5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinonitrile dihydrochloride (81 mg, yield 88%) was obtained as a white powder from tert-butyl {[5-cyano-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (100 mg, 0.25 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.95 (6H, d, J = 6.6 Hz), 2.21-2.27(1H, m), 2.42 (3H, s), 2.71 (3H, s), 2.89 (2H, d, J = 6.9 Hz), 3.82 (2H, d, J = 5.4 Hz), 7.33-7.40 (4H, m), 8.50 (3H, brs).

Example 95

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]urea dihydrochloride

1) To a solution (3 mL) of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) in N,N-dimethylformamide was added triethylamine (170 μl, 1.5 mmol), and diphenylphosphoryl azide (260 μL, 1.5 mmol) was added dropwise under ice-cooling. The mixture was stirred for 30

min. and water was added to the reaction mixture. The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in toluene (3 mL). The mixture was heated under reflux with stirring for 1 hr. 25% Aqueous ammonia (3 mL) was added to the reaction mixture and the mixture was stirred at 100°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. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give tert-butyl {[5-[(aminocarbonyl)amino]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (101 mg, yield 24%) as white crystals.

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.15-2.26 (1H, m), 2.39 (3H, s), 2.56 (3H, s), 2.76 (2H, d, J = 7.2 Hz), 4.10 (2H, d, J = 5.1 Hz), 4.24 (1H, brs), 4.38 (2H, s), 5.50 (1H, s), 7.01 (2H, d, J = 7.5 Hz), 7.24 (2H, d, J = 7.5 Hz).

2) N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]urea dihydrochloride (84 mg, yield 92%) was obtained as a white powder from tert-butyl {[5-[(aminocarbonyl)amino]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (100 mg, 0.23 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.98 (6H, d, J = 5.4 Hz), 2.14-2.19 (1H, m), 2.40 (3H, s), 2.53 (3H, s), 3.0. (2H, brs), 3.80 (2H, brs), 3.83 (1H, brs), 5.94 (1H, brs), 7.20 (2H, d, J = 7.8Hz), 7.36 (2H, d, J = 7.8 Hz), 8.28 (3H, brs).

Example 96

N'-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N,N-dimethylurea dihydrochloride

1) tert-Butyl {[5-{[(dimethylamino)carbonyl]amino}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (158 mg, yield 35%) was obtained as a white powder from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and 2M dimethylamine tetrahydrofuran solution (0.6 mL, 1.2 mmol) according to a method similar to the method of Example 95-1).

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.15-2.25 (1H, m), 2.41 (3H, s), 2.51 (3H, s), 2.71 (6H, s), 2.75 (2H, d, J = 9.0 Hz), 4.08 (2H, d, J = 5.1 Hz), 4.23 (1H, brs), 5.32 (1H, s), 7.02 (2H, d, J = 7.8 Hz), 7.24 (2H, d, J = 7.8 Hz).

2) N'-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N,N-dimethylurea dihydrochloride (108 mg, yield 73%) was obtained as a white powder from tert-butyl {[5-{[(dimethylamino)carbonyl]amino}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (158 mg, 0.35 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.98 (6H, d, J = 6.3 Hz), 2.17-2.20 (1H, m), 2.39 (3H, s), 2.64 (9H, s), 3.09 (2H, brs), 3.83 (2H, brs), 7.20 (2H, d, J = 7.8 Hz), 7.31 (2H, d, J = 7.8 Hz), 7.86 (1H, brs), 8.39 (3H, brs).

Example 97

benzyl [5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbamate dihydrochloride

1) Benzyl [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbamate (1600 mg, yield 35%) was obtained as a white powder from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (3700 mg, 8.9 mmol) and benzyl alcohol (2.3 mL, 10.7 mmol) according to a method similar to the method of Example 95-1).

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.13-

methylphenyl)pyridin-3-yl]amino}sulfonyl)-4-methyl-1,3-thiazol-2-yl]acetamide dihydrochloride

N-[5-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}sulfonyl)-4-methyl-1,3-thiazol-2-yl]acetamide dihydrochloride (58 mg, yield 39%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (100 mg, 0.26 mmol) and 2-(acetylamino)-4-methyl-1,3-thiazole-5-sulfonyl chloride (76 mg, 0.3 mmol) according to a method similar to the method of Example 99.

^{1}H-NMR (DMSO-d_6) δ:0.94 (6H, d, J = 6.6 Hz), 2.02 (3H, s), 2.19 (3H, s), 2.18-2.23 (1H, m), 2.27 (3H, s), 2.53 (3H, s), 2.84 (2H, brs), 3.69 (2H, brs), 6.92-6.97 (4H, m), 8.10 (3H, brs), 9.89 (1H, brs).

Example 101

{[5-(aminomethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amine trihydrochloride

1) A mixture of tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.16 g, 2.91 mmol), triethylamine (0.8 mL, 5.82 mmol) and tetrahydrofuran (15 mL) was cooled to 0°C and methanesulfonyl chloride (500 mg, 4.37 mmol) was added dropwise. After stirring at room temperature for 30 min., the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to give [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl methanesulfonate as a crude product. The crude product was dissolved in N,N-dimethylformamide (30 mL) and sodium azide (379 mg, 5.82 mmol) was added. The mixture was stirred at 80°C for 30 min. The reacti n mixture was diluted with ethyl acetate (100 mL) and washed with saturated brine. The organic layer was dried over

methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (50 mg, 0.13 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.94 (6H, d, J = 6.6 Hz), 1.97-2.08 (1H, m), 2.42 (3H, s), 2.65 (3H, s), 2.99 (2H, s), 3.69 (2H, s), 5.40 (3H, brs), 7.26 (2H, d, J = 8.1Hz), 7.44 (2H, d, J = 8.1 Hz), 8.38 (3H, brs).

Example 99

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methanesulfonamide dihydrochloride

To a solution of tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (100 mg, 0.26 mmol) in tetrahydrofuran (2 mL) was added triethylamine (54 μL, 0.39 mmol) and methanesulfonyl chloride (30 μL, 0.39 mmol) was added at room temperature. Then the mixture was stirred for 3 hrs. 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. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give an oil. To a solution of the oil in ethyl acetate (1 mL) was added 4N hydrogen chloride ethyl acetate solution (1 mL) and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from hexane to give N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methanesulfonamide dihydrochloride (25 mg, yield 22%) as a white powder.

^{1}H-NMR (DMSO-d_6) δ:0.97 (6H, d, J = 6.6 Hz), 2.18-2.24 (1H, m), 2.20 (3H, s), 2.39 (3H, s), 2.71 (3H, s), 2.96 (2H, s), 3.79 (2H, s), 7.28 (2H, d, J = 6.9Hz), 7.34 (2H, d, J = 6.9 Hz), 8.32 (3H, brs), 9.27 (1H, brs).

Example 100

N-[5-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-

methylphenyl)pyridin-3-yl]amino}sulfonyl)-4-methyl-1,3-thiazol-2-yl]acetamide dihydrochloride

N-[5-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}sulfonyl)-4-methyl-1,3-thiazol-2-yl]acetamide dihydrochloride (58 mg, yield 39%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (100 mg, 0.26 mmol) and 2-(acetylamino)-4-methyl-1,3-thiazole-5-sulfonyl chloride (76 mg, 0.3 mmol) according to a method similar to the method of Example 99.

^{1}H-NMR (DMSO-d_6) δ:0.94 (6H, d, J = 6.6 Hz), 2.02 (3H, s), 2.19 (3H, s), 2.18-2.23 (1H, m), 2.27 (3H, s), 2.53 (3H, s), 2.84 (2H, brs), 3.69 (2H, brs), 6.92-6.97 (4H, m), 8.10 (3H, brs), 9.89 (1H, brs).

Example 101

{[5-(aminomethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amine trihydrochloride

1) A mixture of tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.16 g, 2.91 mmol), triethylamine (0.8 mL, 5.82 mmol) and tetrahydrofuran (15 mL) was cooled to 0°C and methanesulfonyl chloride (500 mg, 4.37 mmol) was added dropwise. After stirring at room temperature for 30 min., the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to give [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl methanesulfonate as a crude product. The crude product was dissolved in N,N-dimethylformamide (30 mL) and sodium azide (379 mg, 5.82 mmol) was added. The mixture was stirred at 80°C for 30 min. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated brine. The organic layer was dried over

anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to give a residue. A mixture of the obtained residue, 10% palladium-carbon (304 mg, 0.291 mmol) and ethanol (15 mL) was stirred under a hydrogen atmosphere at room temperature for 2 hrs. After filtration, the solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give tert-butyl {[5-(aminomethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (690 mg, yield 60%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ:0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 1.41 (2H, brs), 2.14-2.23 (1H, m), 2.41 (3H, s), 2.64 (3H, s), 4.02 (2H, d, J = 5.1 Hz), 4.18 (1H, brs), 7.02 (2H, d, J = 7.9 Hz), 7.25 (2H, d, J = 7.0 Hz).

2) {[5-(Aminomethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amine trihydrochloride (204 mg, yield 99%) was obtained as a white powder from tert-butyl {[5-(aminomethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (200 mg, 0.503 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.97 (6H, d, J = 6.6 Hz), 2.13-2.24 (1H, m), 2.43 (3H, s), 2.50 (3H, s), 2.98 (2H, brs), 3.76 (4H, brs), 7.34-7.45 (4H, m), 8.51 (6H, brs).

Example 102

N-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}-4-(methylsulfonyl)benzenesulfonamide dihydrochloride

1) To a solution (10 mL) of tert-butyl {[5-(aminomethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (290 mg, 0.729 mmol) and triethylamine (0.15 mL, 1.09 mmol) in tetrahydrofuran was added 4-(methylsulfonyl)benzenesulfonyl chloride (223 mg, 0.875 mmol) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate (100 mL) and

washed successively with saturated aqueous sodium hydrogen carbonate and saturated brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained yellow solid was washed with diisopropyl ether to give tert-butyl ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[({[4-(methylsulfonyl)phenyl]sulfonyl}amino)methyl]pyridin-3-yl}methyl)carbamate (391 mg, yield 87%) as a yellow powder.
^{1}H-NMR ($CDCl_3$) δ:0.95 (6H, d, J = 6.6 Hz), 1.36 (9H, s), 2.13-2.22 (1H, m), 2.41 (3H, s), 2.61 (3H, s), 2.73 (2H, d, J = 7.4 Hz), 3.08 (3H, s), 3.83 (2H, d, J = 5.8 Hz), 3.97 (2H, d, J = 4.9 Hz), 4.11-4.20 (2H, m), 6.84 (2H, d, J = 8.1 Hz), 7.13 (2H, d, J = 7.7 Hz), 7.77 (2H, d, J = 8.7 Hz), 7.98 (2H, d, J = 8.5 Hz).

2) N-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}-4-(methylsulfonyl)benzenesulfonamide dihydrochloride (370 mg, yield 99%) was obtained as a yellow powder from tert-butyl ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[({[4-(methylsulfonyl)phenyl]sulfonyl}amino)methyl]pyridin-3-yl}methyl)carbamate (391 mg, 0.635 mmol) according to a method similar to the method of Example 2-3).
^{1}H-NMR (DMSO-d_6) δ:0.96 (6H, d, J = 6.6 Hz), 2.11-2.19 (1H, m), 2.35 (3H, s), 2.50 (3H, s), 2.70-2.82 (2H, m), 3.31 (3H, s), 3.66 (2H, brs), 3.72 (2H, brs), 7.11-7.21 (4H, m), 7.83 (2H, dd, J = 8.3, 1.3 Hz), 8.08 (2H, d, J = 8.1 Hz), 8.31 (3H, brs).

Example 103

ethyl ({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amino)acetate trihydrochloride

1) To a solution of [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl methanesulfonate (300 mg, 0.63 mmol) in tetrahydrofuran (5 mL) were added triethylamine (223 μL, 1.6 mmol) and glycine ethyl ester hydrochloride (100 mg, 0.7 mmol) and the mixture was

stirred at 60°C for 3 days. 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. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give ethyl ({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amino)acetate (185 mg, yield 61%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:0.95 (6H, d, J = 6.6 Hz), 1.22 (3H, t, J = 6.9Hz), 1.38 (9H, s), 2.15-2.22 (1H, m), 2.41 (3H, s), 2.67 (3H, s), 2.73 (2H, d, J = 7.2Hz), 3.18 (2H, s), 3.43 (2H, s), 4.02 (2H, s), 4.09 (2H, q, J = 6.9Hz), 4.18 (1H, brs), 7.03 (2H, d, J =7.8Hz), 7.25 (2H, d, J = 7.8 Hz).

2) Ethyl ({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amino)acetate trihydrochloride (57 mg, yield 95%) was obtained as a white powder from ethyl ({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amino)acetate (60 mg, 0.12 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.97 (6H, d, J = 6.6 Hz), 1.18 (3H, t, J = 6.9 Hz), 2.11-2.24 (1H, m), 2.42 (3H, s), 2.92 (3H, brs), 3.03 (2H, brs), 3.61 (2H, s), 3.72 (2H, brs), 4.06 (2H, s), 4.08 (2H, q, J = 6.9 Hz), 7.35 (2H, d, J =8.1Hz), 7.40 (2H, d, J = 8.1 Hz), 8.43 (3H, brs).

Example 104

({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amino)acetic acid trihydrochloride

1) To a solution of ethyl ({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amino)acetate (100 mg, 0.2 mmol) in ethanol (3 mL) was added 8N aqueous sodium hydroxide

solution (3 mL) and the mixture was stirred at 80°C for 15 hrs. 1N Hydrochloric acid was added to neutralize 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. The solvent was evaporated under reduced pressure to give ({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amino)acetic acid (92 mg, yield 99%) as a white powder.

^{1}H-NMR (DMSO-d_6) δ:0.91 (6H, d, J = 6.3 Hz), 1.35 (9H, s), 2.11-2.24 (1H, m), 2.36 (3H, s), 2.54 (2H, s), 2.57 (3H, s), 2.97 (2H, s), 3.39 (2H, s), 3.76 (2H, s), 6.78 (1H, brs), 7.18 (2H, d, J =7.8Hz), 7.22 (2H, d, J = 7.8 Hz).

2) ({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amino)acetic acid trihydrochloride (75 mg, yield 80%) was obtained as a white powder from ({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amino)acetic acid (90 mg, 0.2 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.97 (6H, d, J = 6.6 Hz), 2.14-2.21 (1H, m), 2.42 (3H, s), 2.89 (3H, s), 3.01 (2H, brs), 3.52 (2H, s), 3.72 (2H, s), 4.04 (2H, s), 7.35 (2H, d, J =8.1 Hz), 7.39 (2H, d, J = 8.1 Hz), 8.37 (3H, brs), 9.29 (1H, brs).

Example 105

4-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}-2-piperazinone trihydrochloride

1) tert-Butyl ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(3-oxo-1-piperazinyl)methyl]pyridin-3-yl}methyl)carbamate (78 mg, yield 77%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl methanesulfonate (300 mg, 0.63 mmol) and 2-piperazinone (65 mg, 0.65 mmol) according to a

method similar to the method of Example 103-1).

^{1}H-NMR ($CDCl_3$) δ:0.96 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.14-2.23 (1H, m), 2.49 (5H, s), 2.64 (3H, s), 2.73 (2H, d, J = 7.2Hz), 2.89 (2H, s), 3.22 (2H, brs), 3.28 (2H, s), 4.01 (2H, d, J = 5.1Hz), 4.20 (1H, brs), 5.69 (1H, brs), 6.96 (2H, d, J = 7.8 Hz), 7.21 (2H, d, J = 7.8 Hz).

2) 4-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}-2-piperazinone trihydrochloride (64 mg, yield 87%) was obtained as a white powder from tert-butyl ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(3-oxo-1-piperazinyl)methyl]pyridin-3-yl}methyl)carbamate (75 mg, 0.15 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.98 (6H, d, J = 6.6 Hz), 1.91 (2H, s), 2.09-2.14 (1H, m), 2.42 (3H, s), 3.00 (3H, brs), 3.18 (4H, brs), 3.75 (2H, brs), 7.30 (2H, d, J = 7.5 Hz), 7.41 (2H, d, J = 7.5 Hz), 7.41 (1H, brs), 8.52 (3H, brs).

Example 106

3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}-2,4-imidazolidinedione dihydrochloride

1) To a solution of tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (100 mg, 0.25 mmol), hydantoin (38 mg, 0.38 mmol) and tributylphosphine (95 μL, 0.38 mmol) in tetrahydrofuran (3 mL) was added 1,1'-(azodicarbonyl)dipiperidine (96 mg, 0.38 mmol) and the mixture was stirred at room temperature for 4 hrs. The reaction mixture was concentrated and insoluble materials were filtered off. The filtrate was purified by silica gel column chromatography to give tert-butyl {[5-[(2,5-dioxo-1-imidazolidinyl)methyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (68 mg, yield 57%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:0.95 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.11-

2.26 (1H, m), 2.39 (3H, s), 2.55 (3H, s), 2.73 (2H, d, J = 7.5 Hz), 3.77 (2H, s), 3.99 (2H, d, J = 5.1 Hz), 4.23 (1H, brs), 4.46 (2H, s), 5.10 (1H, brs), 7.07 (2H, d, J = 7.8 Hz), 7.23 (2H, d, J = 7.8 Hz).

2) 3-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}-2,4-imidazolidinedione dihydrochloride (54 mg, yield 95%) was obtained as a white powder from tert-butyl {[5-[(2,5-dioxo-1-imidazolidinyl)methyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.96 (6H, d, J = 6.6 Hz), 2.14-2.19 (1H, m), 2.37 (3H, s), 2.84 (3H, s), 3.11 (2H, brs), 3.71 (4H, s), 4.35 (2H, s), 7.18 (2H, d, J = 8.1 Hz), 7.33 (2H, d, J = 7.8 Hz), 8.00 (1H, brs), 8.30 (1H, brs).

Example 107

1-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}-2,5-piperazinedione dihydrochloride

1) To a solution of Z-glycine (1.2 g, 6 mmol) and N,N-dimethylformamide (10 μL) in tetrahydrofuran (5 mL) was added oxalyl chloride (530 μL, 6 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was added dropwise to a solution of ethyl ({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amino)acetate (1.4 g, 3 mmol), pyridine (970 μL, 12 mmol) and 4-dimethylaminopyridine (5 mg) in tetrahydrofuran (10 mL) under ice-cooling and the mixture was stirred for 3 hrs. 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. The solvent was evaporated under reduced pressure and the obtained il was dissolved in ethanol (10 mL). 5% Palladium-carbon (100 mg) was added and the mixture was

stirred under a hydrogen atmosphere at room temperature for 2 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give tert-butyl {[5-[(2,5-dioxo-1-piperazinyl)methyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (35 mg, yield 2.4%) as a white powder.

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.18-2.24 (1H, m), 2.40 (3H, s), 2.51 (3H, s), 2.76 (2H, d, J = 7.5Hz), 3.47 (2H, s), 3.93 (2H, s), 4.03 (2H, d, J = 5.1 Hz), 4.24 (1H, brs), 4.51 (2H, s), 5.88 (1H, brs), 6.98 (2H, d, J = 7.5 Hz), 7.25 (2H, d, J = 7.5 Hz).

2) 1-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}-2,5-piperazinedione dihydrochloride (14 mg, yield 60%) was obtained as a white powder from tert-butyl {[5-[(2,5-dioxo-1-piperazinyl)methyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.97 (6H, d, J = 6.6 Hz), 2.15-2.19 (1H, m), 2.39 (3H, s), 2.69 (3H, s), 3.25 (2H, s), 3.67 (2H, s), 3.73 (2H, brs), 4.31 (2H, s), 7.18 (2H, d, J = 8.1 Hz), 7.37 (2H, d, J = 7.8 Hz), 8.06 (1H, brs), 8.24 (3H, brs).

Example 108

{[2-isobutyl-4-(4-methylphenyl)-6-phenylpyridin-3-yl]methyl}amine dihydrochloride

1) To a solution (140 mL) of acetophenone (8.40 g, 70 mmol) and p-tolualdehyde (8.40 g, 70 mmol) in ethanol was added sodium hydroxide (7.0 g, 175 mmol) and the mixture was stirred for 3 days. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained yellow solid was washed with diisopropyl ether to give (2E)-3-(4-

methylphenyl)-1-phenylprop-2-en-1-one (9.12 g, yield 59%) as a yellow powder.

^{1}H-NMR ($CDCl_3$) δ:2.40 (3H, s), 7.23 (2H, d, J = 8.1 Hz), 7.47-7.62 (6H, m), 7.80 (1H, d, J = 15.8 Hz), 8.00-8.03 (2H, m).

2) A mixture of 5-methyl-3-oxohexanenitrile (5.0 g, 40 mmol), acetic acid (2.3 mL, 40 mmol), ammonium acetate (15.4 g, 200 mmol) and toluene (250 mL) was heated under reflux using a Dean-Stark trap for 12 hrs. The reaction mixture was allowed to cool to room temperature, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give a residue (4.5 g). The residue (2.25 g) was dissolved in ethanol (100 mL) and (2E)-3-(4-methylphenyl)-1-phenylprop-2-en-1-one (3.69 g, 16.6 mmol) and sodium hydroxide (0.8 g, 20 mmol) were added. The mixture was heated under reflux for 3 hrs. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated aqueous ammonium chloride. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give 2-isobutyl-4-(4-methylphenyl)-6-phenylnicotinonitrile (2.68 g, yield 49%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ:1.07 (6H, d, J = 6.8 Hz), 2.35-2.48 (4H, m), 3.06 (2H, d, J = 7.2 Hz), 7.35 (2H, d, J = 7.9 Hz), 7.49-7.56 (5H, m), 7.67 (1H, s), 8.07-8.13 (1H, m).

3) {[2-Isobutyl-4-(4-methylphenyl)-6-phenylpyridin-3-yl]methyl}amine (1.70 g, yield 63%) was obtained as a yellow oil from 2-isobutyl-4-(4-methylphenyl)-6-phenylnicotinonitrile (2.65 g, 8.12 mmol) according to a method similar to the method of Example 1-4). The oil was dissolved in 4N hydrogen chloride 1,4-dioxane solution (20 mL) and the solvent was evaporated under reduced pressure. The obtained yellow solid was washed with diisopropyl ether to give {[2-isobutyl-4-(4-methylphenyl)-6-phenylpyridin-3-yl]methyl}amine dihydrochloride (1.99 g,

yield 96%) as a yellow powder.

^{1}H-NMR (DMSO-d_6) δ:1.03 (6H, d, J = 6.6 Hz), 2.34-2.41 (4H, m), 2.94 (2H, d, J = 7.0 Hz), 4.00 (2H, d, J = 5.5 Hz), 7.36 (2H, d, J = 8.2 Hz), 7.41 (2H, d, J = 8.3 Hz), 7.47-7.54 (3H, m), 7.70 (1H, s), 8.15 (2H, dd, J = 7.9, 1.5 Hz), 8.43 (3H, brs).

Example 109

5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid maleate

5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.50 g, 4.80 mmol) was dissolved in a mixed solvent of water (15 mL) and acetonitrile (15 mL) and the mixture was heated under reflux for 10 min. Maleic acid (558 mg, 4.80 mmol) was added to the obtained solution and the mixture was stirred at the same temperature for 10 min. Acetonitrile (200 mL) was added to the obtained solution, and the mixture was allowed to cool to room temperature and stirred at 0°C for 30 min. The precipitated solid was collected by filtration and washed with acetonitrile (30 mL) to give 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid maleate (667 mg, yield 32%) as a white powder.

^{1}H-NMR (DMSO-d_6) δ:0.96 (6H, d, J = 6.6 Hz), 2.18-2.27 (1H, m), 2.37 (3H, s), 2.74 (2H, d, J = 7.0 Hz), 3.79 (2H, s), 6.01 (2H, s), 7.19 (2H, d, J = 7.9 Hz), 7.29 (2H, d, J = 7.5 Hz).

Example 110

5-(aminomethyl)-6-(methoxymethyl)-2-methyl-4-(4-methylphenyl)nicotinic acid dihydrochloride

1) A solution (40 mL) of methyl 4-methoxyacetoacetate (5.85 g, 40 mmol), p-tolualdehyde (4.81 g, 40 mmol), piperidine (340 mg, 4 mmol) and acetic acid (240 mg, 4 mmol) in isopropanol was stirred at room temperature for 3 days. The solvent was evaporated under reduced pressure to give a residue. 3-Methyl 5-tert-butyl 2-(methoxymethyl)-6-methyl-4-(4-methylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (5.85 g, yield 50%) was obtained as a yellow oil from the obtained residue and tert-

butyl 3-aminocrotonate (4.71 g, 30.0 mol) according to a method similar to the method of Example 1-2). That is, the aforementioned residue and tert-butyl 3-aminocrotonate were dissolved in methanol (30 mL) and the mixture was heated under reflux for 1.5 hrs. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give 3-methyl 5-tert-butyl 2-(methoxymethyl)-6-methyl-4-(4-methylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

^{1}H-NMR ($CDCl_3$) δ:1.40 (9H, s), 2.28 (3H, s), 2.32 (3H, s), 3.45-3.46 (3H, m), 3.62-3.63 (3H, m), 4.55-4.76 (2H, m), 4.89-4.95 (1H, m), 6.94 (1H, brs), 7.01 (2H, d, J = 7.7 Hz), 7.15 (2H, d, J = 8.1 Hz).

2) 3-Methyl 5-tert-butyl 2-(methoxymethyl)-6-methyl-4-(4-methylphenyl)pyridine-3,5-dicarboxylate (3.78 g, yield 65%) was obtained as a yellow oil from 3-methyl 5-tert-butyl 2-(methoxymethyl)-6-methyl-4-(4-methylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (5.85 g, 15.1 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:1.23 (9H, s), 2.37 (3H, s), 2.61 (3H, s), 3.36 (3H, s), 3.54 (3H, s), 4.66 (2H, s), 7.13-7.15 (2H, m), 7.17-7.19 (2H, m).

3) A suspension of 3-methyl 5-tert-butyl 2-(methoxymethyl)-6-methyl-4-(4-methylphenyl)pyridine-3,5-dicarboxylate (3.78 g, 9.81 mmol) in toluene (50 mL) was cooled to -78°C and 1.50 M diisobutylaluminum hydride toluene solution (25 mL, 24.5 mmol) was added dropwise over 15 min. The mixture was stirred at -78°C for 30 min., allowed to warm to 0°C and further stirred for 10 min. Methanol (0.5 mL) was added to the reaction mixture and sodium sulfate 10 hydrate (8.1 g, 9.8 mmol) was added. The mixture was stirred at room temperature for 1 hr. The insoluble material was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl 5-

(hydroxymethyl)-6-(methoxymethyl)-2-methyl-4-(4-methylphenyl)nicotinate (810 mg, yield 23%) as a yellow oil.
^{1}H-NMR ($CDCl_3$) δ:1.21 (9H, s), 2.39 (3H, s), 2.59 (3H, s), 3.50 (3H, s), 4.39 (2H, d, J = 6.8 Hz), 4.76 (2H, s), 7.21 (4H, s).

4) A mixture of tert-butyl 5-(hydroxymethyl)-6-(methoxymethyl)-2-methyl-4-(4-methylphenyl)nicotinate (810 mg, 2.27 mmol), triethylamine (0.63 mL, 4.54 mmol) and tetrahydrofuran (30 mL) was cooled to 0°C and methanesulfonyl chloride (0.26 mL, 3.40 mmol) was added dropwise. After stirring at room temperature for 30 min., the reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated aqueous sodium hydrogen carbonate. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (20 mL) and sodium azide (296 mg, 4.54 mmol) was added. The mixture was stirred at 80°C for 1 hr. Ethyl acetate was added to the reaction mixture, and the mixture was washed successively with water and saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. A mixture of the residue, 10% palladium-carbon (242 mg, 0.227 mmol) and ethanol (30 mL) was stirred under a hydrogen atmosphere at room temperature for 30 min. After filtration, the solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give tert-butyl 5-(aminomethyl)-6-(methoxymethyl)-2-methyl-4-(4-methylphenyl)nicotinate (600 mg, yield 74%) as a yellow oil.
^{1}H-NMR ($CDCl_3$) δ:1.19 (9H, s), 2.40 (3H, s), 2.57 (3H, s), 3.48 (3H, s), 3.63 (2H, s), 4.69 (2H, s), 7.12 (2H, d, J = 8.1 Hz), 7.23 (2H, d, J = 7.7 Hz).

5) 5-(Aminomethyl)-6-(methoxymethyl)-2-methyl-4-(4-methylphenyl)nicotinic acid dihydrochloride (533 mg, yield 84%) was obtained as a white powder from tert-butyl 5-(aminomethyl)-6-(methoxymethyl)-2-methyl-4-(4-methylphenyl)nicotinate (600

mg, 1.69 mmol) according to a method similar to the method of Example 24-i).

^{1}H-NMR (DMSO-d_6) δ:2.37 (3H, s), 2.53 (3H, s), 3.41 (3H, s), 3.86 (2H, d, J = 5.7 Hz), 4.76 (2H, s), 7.24 (2H, d, J = 8.1 Hz), 7.30 (2H, d, J = 8.1 Hz), 8.10 (3H, brs).

Example 111

5,6-bis(aminomethyl)-2-methyl-4-(4-methylphenyl)nicotinic acid trihydrochloride

1) Ethyl 3-amino-4-[(tert-butoxycarbonyl)amino]but-2-enoate (5.37g, yield 99%) was obtained as a yellow oil from ethyl 4-[(tert-butoxycarbonyl)amino]-3-oxobutanoate (5.4 g, 22.0 mmol) according to a method similar to the method of Example 108-2).

^{1}H-NMR ($CDCl_3$) δ:1.26 (3H, t, J = 7.2 Hz), 1.46 (9H, s), 3.77 (2H, d, J = 6.6 Hz), 4.12 (2H, q, J = 7.1 Hz), 4.55 (1H, s).

2) A mixture of tert-butyl acetoacetate (4.75 g, 30 mmol), p-tolualdehyde (4.51 g, 37.5 mmol), piperidine (0.30 mL, 3.00 mmol) and ethanol (0.2 mL) was stirred at room temperature for one day. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue and ethyl 3-amino-4-[(tert-butoxycarbonyl)amino]but-2-enoate (5.37 g, 22.0 mmol) were stirred at 80°C for 30 min. and further stirred at 130°C for 3 hrs. The obtained mixture was purified by silica gel column chromatography to give 3-ethyl 5-tert-butyl 2-{[(tert-butoxycarbonyl)amino]methyl}-6-methyl-4-(4-methylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.95 g, yield 18%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ:1.22-1.28 (3H, m), 1.40 (9H, s), 1.46 (9H, s), 2.27 (6H, s), 4.04-4.18 (3H, m), 4.37-4.44 (1H, m), 4.87 (1H, s), 5.35 (1H, brs), 7.01 (2H, d, J = 7.9 Hz), 7.15 (2H, d, J = 8.1 Hz).

3) 3-Ethyl 5-tert-butyl 2-{[(tert-butoxycarbonyl)amino]methyl}-6-methyl-4-(4-methylphenyl)pyridine-3,5-dicarboxylate (1.94 g,

yield 99%) was obtained as a yellow oil from 3-ethyl 5-tert-butyl 2-{[(tert-butoxycarbonyl)amino]methyl}-6-methyl-4-(4-methylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.95 g, 4.01 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) δ:0.93 (3H, t, J = 7.2 Hz), 1.23 (9H, s), 1.47 (9H, s), 2.37 (3H, s), 2.61 (3H, s), 4.02 (2H, q, J = 7.1 Hz), 4.50 (2H, d, J = 4.7 Hz), 5.87 (1H, brs), 7.13 (2H, d, J = 8.3 Hz), 7.17 (2H, d, J = 8.3 Hz).

4) tert-Butyl 6-{[(tert-butoxycarbonyl)amino]methyl}-5-(hydroxymethyl)-2-methyl-4-(4-methylphenyl)nicotinate (1.45 g, yield 82%) was obtained as a yellow oil from 3-ethyl 5-tert-butyl 2-{[(tert-butoxycarbonyl)amino]methyl}-6-methyl-4-(4-methylphenyl)pyridine-3,5-dicarboxylate (1.94 g, 4.00 mmol) according to a method similar to the method of Example 110-3).

^{1}H-NMR ($CDCl_3$) δ:1.20 (9H, s), 1.46 (9H, s), 2.39 (3H, s), 2.57 (3H, s), 3.38 (1H, brs), 4.46 (2H, d, J = 6.0 Hz), 4.54 (2H, d, J = 5.8 Hz), 5.87 (1H, brs), 7.18 (2H, d, J = 8.3 Hz), 7.21 (2H; d, J = 8.3 Hz).

5) tert-Butyl 5-(aminomethyl)-6-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)nicotinate (580 mg, yield 40%) was obtained as a white powder from tert-butyl 6-{[(tert-butoxycarbonyl)amino]methyl}-5-(hydroxymethyl)-2-methyl-4-(4-methylphenyl)nicotinate (1.45 g, 3.28 mmol) according to a method similar to the method of Example 110-4).

^{1}H-NMR ($CDCl_3$) δ:1.18 (9H, s), 1.49 (9H, s), 2.39 (3H, s), 2.56 (3H, s), 3.62 (2H, s), 4.58 (2H, d, J = 4.7 Hz), 6.22 (1H, brs), 7.10 (2H, d, J = 8.1 Hz), 7.22 (2H, d, J = 7.9 Hz).

6) 5,6-Bis(aminomethyl)-2-methyl-4-(4-methylphenyl)nicotinic acid trihydrochloride (510 mg, yield 99%) was obtained as a yellow solid from tert-butyl 5-(aminomethyl)-6-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)nicotinate (580 mg, 1.31 mmol) according to a

method similar to the method of Example 24-1).

^{1}H-NMR (DMSO-d_6) δ:2.37 (3H, s), 2.57 (3H, s), 3.84-3.89 (2H, m), 4.51-4.61 (2H, m), 7.23 (2H, d, J = 7.9 Hz), 7.31 (2H, d, J = 7.9 Hz), 8.42 (3H, brs), 8.54 (3H, brs).

Example 112

5-(aminomethyl)-6-hydroxy-2-methyl-4-(4-methylphenyl)nicotinic acid hydrochloride

1) A mixture of tert-butyl acetoacetate (4.75 g, 30 mmol), p-tolualdehyde (4.51 g, 37.5 mmol), piperidine (0.30 mL, 3.00 mmol) and ethanol (0.2 mL) was stirred at room temperature for one day. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue, ethyl cyanoacetate (6.79 g, 60.0 mmol) and ammonium acetate (11.6 g, 150 mmol) were stirred at 140°C for 3 hrs. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated aqueous sodium hydrogen carbonate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give tert-butyl 5-cyano-6-hydroxy-2-methyl-4-(4-methylphenyl)nicotinate (0.87 g, yield 9%) as a white solid.

^{1}H-NMR ($CDCl_3$) δ:1.19 (9H, s), 2.41 (3H, s), 2.57 (3H, s), 7.24-7.31 (4H, m).

2) tert-Butyl 5-(aminomethyl)-6-hydroxy-2-methyl-4-(4-methylphenyl)nicotinate was obtained as a white solid from tert-butyl 5-cyano-6-hydroxy-2-methyl-4-(4-methylphenyl)nicotinate (0.50 g, 1.54 mmol) according to a method similar to the method of Example 1-4). Subsequently, tert-butyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-hydroxy-2-methyl-4-(4-methylphenyl)nicotinate (210 mg, yield 32%) was obtained as a colorless oil according to a method similar to the method of Example 2-1).

^{1}H-NMR ($CDCl_3$) δ:1.13 (9H, s), 1.39 (9H, s), 2.38 (3H, s), 2.43 (3H, s), 4.02 (2H, d, J = 5.8 Hz), 7.10 (2H, d, J = 7.9 Hz), 7.22 (2H, d, J = 7.9 Hz), 12.39 (1H, brs).

3) 5-(Aminomethyl)-6-hydroxy-2-methyl-4-(4-methylphenyl)nicotinic acid hydrochloride (167 mg, yield 99%) was obtained as a white solid from tert-butyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-hydroxy-2-methyl-4-(4-methylphenyl)nicotinate (210 mg, 0.490 mmol) according to a method similar to the method of Example 24-1).

^{1}H-NMR (DMSO-d_6) δ:2.33 (3H, s), 2.35 (3H, s), 3.51 (2H, s), 7.15 (2H, d, J = 7.9 Hz), 7.26 (2H, d, J = 7.9 Hz), 7.94 (3H, brs), 12.42 (1H, s), 12.74 (1H, s).

Example 113

5-(aminomethyl)-N,6-diisobutyl-2-methyl-4-(4-methylphenyl)nicotinamide ditrifluoroacetate

5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (23.9 mg, 0.06 mmol), isobutylamine (5.3 mg, 0.072 mmol), 1-hydroxy-1H-benzotriazole (11.0 mg, 0.072 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (13.8 mg, 0.072 mmol) were dissolved in a mixed solvent of N,N-dimethylformamide (1.25 mL)-dichloromethane (0.4 mL), and the mixture was stirred at 50°C for 2 days. The reaction mixture was diluted with dichloromethane (3 mL) and washed successively with saturated aqueous sodium hydrogen carbonate (0.5 mL) and saturated brine (0.5 mL). Trifluoroacetic acid (2 mL) was added to the organic layer and the mixture was stirred for 2 hrs. The solvent was evaporated under reduced pressure and the residue was purified by preparative HPLC to give 5-(aminomethyl)-N,6-diisobutyl-2-methyl-4-(4-methylphenyl)nicotinamide ditrifluoroacetate (22.4 mg, yield 63%) as a yellow oil.

EIMS (M+1): 368

The compounds of Examples 114-168 were synthesized from

nicotinic acids and amines corresponding to the following Tables 1-4 according to a method similar to the method of Example 113. The compounds of Examples 162-164 were obtained as free form by neutralizing the resulting trifluoroacetate of nicotinic amides with saturated aqueous sodium hydrogen carbonate.

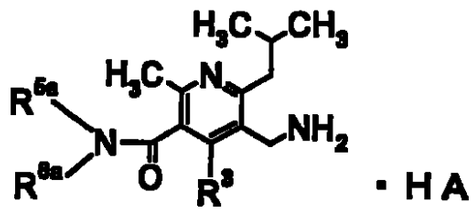


Table 1

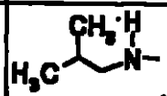
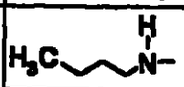
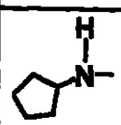
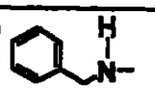
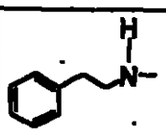
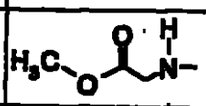
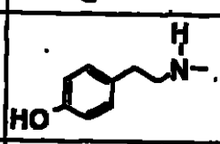
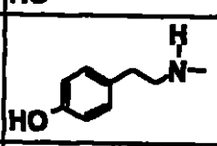
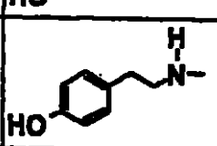
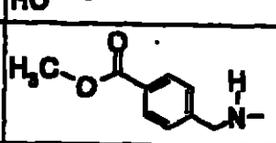
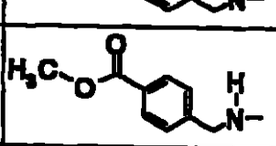
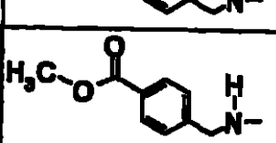
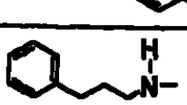
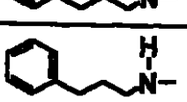
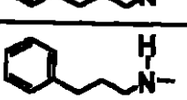
Example	$-NR^{5a}R^{5b}$	$-R^3$	FIMS (M+1)	HA
113		4-Me-Phenyl	368	$2CF_3COOH$
114		4-Me-Phenyl	368	$2CF_3COOH$
115		4-Me-Phenyl	380	$2CF_3COOH$
116		4-Me-Phenyl	402	$2CF_3COOH$
117		4-Me-Phenyl	416	$2CF_3COOH$
118		4-Me-Phenyl	384	$2CF_3COOH$
119		4-Me-Phenyl	432	$2CF_3COOH$
120		4-F-Phenyl	436	$2CF_3COOH$
121		2,6-di-F-Phenyl	454	$2CF_3COOH$
122		4-Me-Phenyl	460	$2CF_3COOH$
123		4-F-Phenyl	464	$2CF_3COOH$
124		2,6-di-F-Phenyl	482	$2CF_3COOH$
125		4-Me-Phenyl	430	$2CF_3COOH$
126		4-F-Phenyl	434	$2CF_3COOH$
127		2,6-di-F-Phenyl	452	$2CF_3COOH$

Table 2

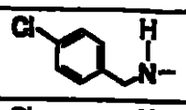
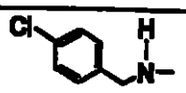
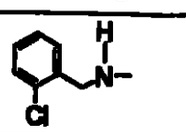
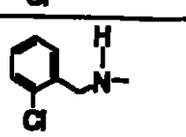
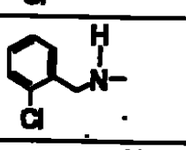
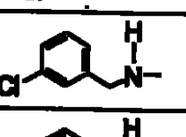
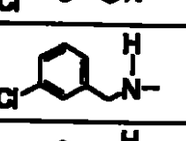
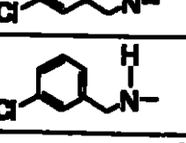
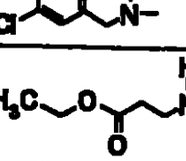
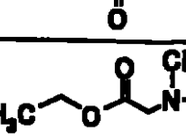
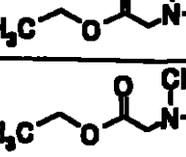
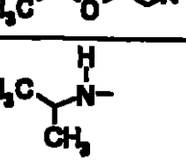
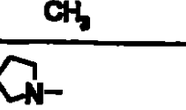
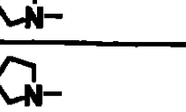
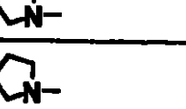
Example	$-NR^{5a}R^{6a}$	$-R^{3}$	EIMS (M+1)	HA
128		4-Me-Phenyl	437	$2CF_3COOH$
129		4-F-Phenyl	440	$2CF_3COOH$
130		2,6-di-F-Phenyl	458	$2CF_3COOH$
131		4-Me-Phenyl	437	$2CF_3COOH$
132		4-F-Phenyl	440	$2CF_3COOH$
133		2,6-di-F-Phenyl	458	$2CF_3COOH$
134		4-Me-Phenyl	437	$2CF_3COOH$
135		4-F-Phenyl	440	$2CF_3COOH$
136		2,6-di-F-Phenyl	458	$2CF_3COOH$
137		4-Me-Phenyl	412	$2CF_3COOH$
138		4-Me-Phenyl	412	$2CF_3COOH$
139		2,6-di-F-Phenyl	434	$2CF_3COOH$
140		4-Me-Phenyl	354	$2CF_3COOH$
141		4-Me-Phenyl	366	$2CF_3COOH$
142		4-F-Phenyl	370	$2CF_3COOH$
143		2,6-di-F-Phenyl	388	$2CF_3COOH$

Table 3

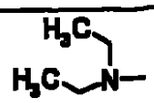
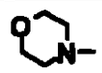
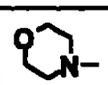
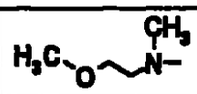
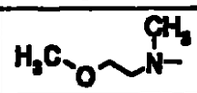
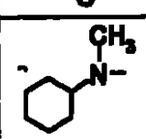
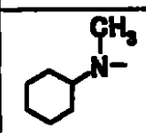
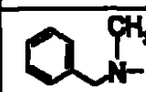
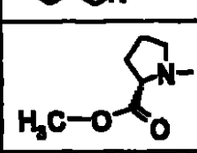
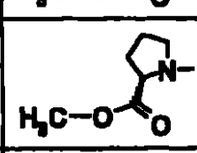
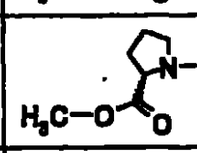
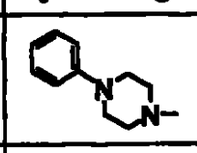
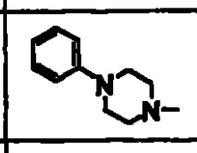
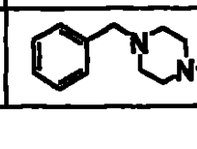
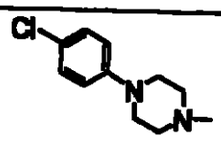
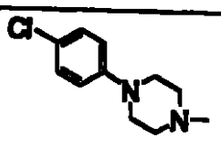
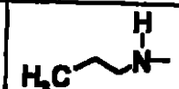
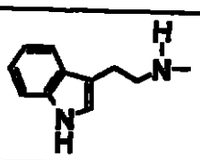
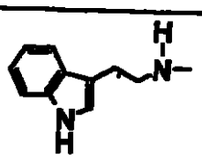
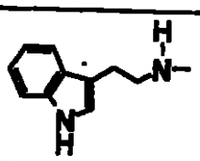
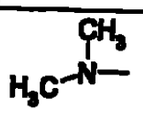
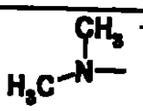
Example	$-NR^{5a}R^{6a}$	$-R^{3}$	EIMS (M+1)	HA
144		4-Me-Phenyl	368	$2CF_3COOH$
145		4-Me-Phenyl	382	$2CF_3COOH$
146		4-F-Phenyl	386	$2CF_3COOH$
147		2,6-di-F-Phenyl	404	$2CF_3COOH$
148		4-Me-Phenyl	384	$2CF_3COOH$
149		2,6-di-F-Phenyl	406	$2CF_3COOH$
150		4-Me-Phenyl	408	$2CF_3COOH$
151		2,6-di-F-Phenyl	430	$2CF_3COOH$
152		4-Me-Phenyl	416	$2CF_3COOH$
153		4-Me-Phenyl	424	$2CF_3COOH$
154		4-F-Phenyl	428	$2CF_3COOH$
155		2,6-di-F-Phenyl	446	$2CF_3COOH$
156		4-Me-Phenyl	457	$3CF_3COOH$
157		4-F-Phenyl	461	$3CF_3COOH$
158		4-Me-Phenyl	471	$3CF_3COOH$

Table 4

Example	$-NR^{5a}R^{6a}$	$-R^3$	EIMS (M+1)	HA
159		4-Me-Phenyl	492	$3CF_3COOH$
160		4-F-Phenyl	496	$3CF_3COOH$
161		4-Me-Phenyl	354	$2CF_3COOH$
162		4-Me-Phenyl	455	
163		4-F-Phenyl	459	
164		2,6-di-F-Phenyl	477	
165		4-F-Phenyl	384	$2CF_3COOH$
166		2,6-di-F-Phenyl	402	$2CF_3COOH$
167		4-F-Phenyl	344	$2CF_3COOH$
168		2,6-di-F-Phenyl	362	$2CF_3COOH$

Example 169

4-(methoxycarbonyl)benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) To a solution (20 mL) of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (2.00 g, 4.85 mmol) in N,N-

dimethylformamide were added methyl 4-(bromomethyl)benzoate (1.22 g, 5.33 mmol) and potassium carbonate (1.01 g, 7.28 mmol) and the mixture was stirred at room temperature for 14 hrs. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give 4-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (2.50 g, yield 92%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ:0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.14-2.25 (1H, m), 2.35 (3H, s), 2.54 (3H, s), 2.78 (2H, d, J = 7.2 Hz), 3.93 (3H, s), 4.12 (2H, d, J = 7.0 Hz), 4.21 (1H, brs), 4.98 (2H, s), 7.01 (2H, d, J = 7.9 Hz), 7.07-7.12 (4H, m), 7.93 (2H, d, J = 8.3 Hz).

2) 4-(Methoxycarbonyl)benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (427 mg, yield 90%) was obtained as a white powder from 4-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.50 g, 0.892 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.96 (6H, d, J = 6,8 Hz), 2.20 (1H, m), 2.34 (3H, s), 2.85 (2H, d, J = 6.6 Hz), 3.80 (2H, d, J = 5.3 Hz), 3.87 (3H, s), 5.07 (2H, s), 7.13-7.16 (4H, m), 7.20 (2H, d, J = 7.9 Hz), 7.87 (2H, d, J = 8.3 Hz), 8.22 (3H, brs).

Example 170

4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]benzoic acid dihydrochloride

1) 4-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]benzoic acid (340 mg, yield 32%) was

obtained as a colorless oil from 4-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.10 g, 1.96 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.16-2.27 (1H, m), 2.35 (3H, s), 2.55 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 4.12 (2H, s), 4.22 (1H, brs), 5.00 (2H, s), 7.02 (2H, d, J = 7.7 Hz), 7.06-7.14 (4H, m), 7.99 (2H, d, J = 8.3 Hz).

2) 4-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]benzoic acid dihydrochloride (326 mg, yield 93%) was obtained as a white powder from 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]benzoic acid (370 mg, 0.677 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.95 (6H, d, J = 6.6 Hz), 2.17-2.27 (1H, m), 2.34 (3H, s), 2.80 (2H, d, J = 7.5 Hz), 3.80 (2H, d, J = 5.8 Hz), 5.06 (2H, s), 7.10-7.14 (4H, m), 7.20 (2H, d, J = 8.1 Hz), 8.10 (3H, brs).

Example 171

2-amino-2-thioxoethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) To a solution (50 mL) of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (3.00 g, 7.27 mmol) in N,N-dimethylformamide were added bromoacetonitrile (0.66 mL, 9.45 mmol) and potassium carbonate (1.51 g, 10.9 mmol) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give cyanomethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-

methylphenyl)nicotinate (2.78 g, yield 85%) as a yellow solid.
^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.19-2.28 (1H, m), 2.39 (3H, s), 2.56 (3H, s), 2.80 (2H, d, J = 7.2 Hz), 4.17 (2H, d, J = 4.9 Hz), 4.24 (1H, brs), 4.50 (2H, s), 7.05 (2H, d, J = 8.1 Hz), 7.24 (2H, d, J = 7.9 Hz).

2) Hydrogen sulfide was blown into a solution (25 mL) of cyanomethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (2.78 g, 6.16 mmol) and triethylamine (0.94 mL, 6.77 mmol) in N,N-dimethylformamide for 1 hr. The solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate (100 mL). The solution was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained yellow solid was washed with diisopropyl ether to give 2-amino-2-thioxoethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (2.81 g, yield 94%) as a yellow brown solid.

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.19-2.28 (1H, m), 2.40 (3H, s), 2.56 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 4.14 (2H, d, J = 4.5 Hz), 4.22 (1H, brs), 4.80 (2H, s), 6.21 (1H, brs), 6.98 (1H, brs), 7.13 (2H, d, J = 7.9 Hz), 7.27 (2H, d, J = 7.5 Hz).

3) 2-Amino-2-thioxoethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (133 mg, yield 70%) was obtained as a yellow solid from 2-amino-2-thioxoethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (200 mg, 0.412 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.97 (6H, d, J = 6.6 Hz), 2.16-2.27 (1H, m), 2.37 (3H, s), 2.58 (3H, s), 2.83 (2H, d, J = 6.2 Hz), 3.83 (2H, d, J = 5.7 Hz), 4.45 (2H, s), 7.21 (2H, d, J = 7.7 Hz), 7.29 (2H, d, J = 7.9 Hz), 8.16 (3H, brs), 8.98 (1H, brs), 9.85 (1H, brs).

Example 172

[4-(ethoxycarbonyl)-1,3-thiazol-2-yl]methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) To a mixed solution of 2-amino-2-thioxoethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (2.02 g, 4.41 mmol) in tetrahydrofuran (30 mL)-saturated aqueous sodium hydrogen carbonate (10 mL) was added benzyl chloroformate (903 mg, 5.30 mmol) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give 2-amino-2-thioxoethyl 5-({[(benzyloxy)carbonyl]amino}methyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (2.00 g, yield 87%) as a pale-yellow solid.

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 2.16-2.25 (1H, m), 2.39 (3H, s), 2.56 (3H, s), 2.81 (2H, d, J = 7.4 Hz), 4.22 (2H, d, J = 5.1 Hz), 4.43 (1H, brs), 4.79 (2H, s), 5.04 (2H, s), 6.23 (1H, brs), 6.97 (1H, brs), 7.11 (2H, d, J = 8.1 Hz), 7.24 (2H, d, J = 7.9 Hz), 7.29-7.36 (5H, m).

2) A solution (70 mL) of 2-amino-2-thioxoethyl 5-({[(benzyloxy)carbonyl]amino}methyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (2.00 g, 3.85 mmol) and ethyl bromopyruvate (1.08 g, 5.00 mmol) in ethanol was heated under reflux for 1 hr. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with saturated aqueous sodium hydrogen carbonate. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give [4-(ethoxycarbonyl)-1,3-thiazol-2-yl]methyl 5-({[(benzyloxy)carbonyl]amino}methyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (2.37 g, yield 100%) as a

colorless oil.

^{1}H-NMR ($CDCl_3$) δ:0.96 (6H, d, J = 6.6 Hz), 1.41 (3H, t, J = 7.2 Hz), 2.10-2.26 (1H, m), 2.32 (3H, s), 2.56 (3H, s), 2.82 (2H, d, J = 7.2 Hz), 4.21 (2H, d, J = 5.3 Hz), 4.44 (2H, q, J = 7.0 Hz), 5.03 (3H, s), 5.22 (2H, s), 7.00 (2H, d, J = 8.1 Hz), 7.07 (2H, d, J = 7.9 Hz), 7.22-7.38 (5H, m), 8.15 (1H, s).

3) [4-(Ethoxycarbonyl)-1,3-thiazol-2-yl]methyl 5-({[(benzyloxy)carbonyl]amino}methyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (2.37 g, 3.85 mmol) was dissolved in 30% hydrogen bromide acetic acid solution (30 mL) and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the obtained residue was dissolved by adding saturated aqueous sodium hydrogen carbonate (30 mL) and tetrahydrofuran (50 mL). Di-tert-butyl dicarbonate (1.02 g, 4.66 mmol) was added and the mixture was stirred at room temperature for 15 hrs. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give [4-(ethoxycarbonyl)-1,3-thiazol-2-yl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.72 g, yield 78%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 1.42 (3H, t, J = 7.2 Hz), 2.17-2.27 (1H, m), 2.33 (3H, s), 2.56 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 4.11-4.16 (2H, m), 4.24 (1H, brs), 4.44 (2H, q, J = 7.2 Hz), 5.22 (2H, s), 7.02 (2H, d, J = 8.1 Hz), 7.10 (2H, d, J = 7.9 Hz), 8.16 (1H, s).

4) [4-(Ethoxycarbonyl)-1,3-thiazol-2-yl]methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (322 mg, yield 90%) was obtained as a white powder from [4-(ethoxycarbonyl)-1,3-thiazol-2-yl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-

methylphenyl)nicotinate (373 mg, 0.643 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.96 (6H, d, J = 6.6 Hz), 1.32 (3H, t, J = 7.2 Hz), 2.18-2.27 (1H, m), 2.29 (3H, s), 2.55 (3H, s), 2.80-2.92 (2H, m), 3.79 (2H, d, J = 5.3 Hz), 4.32 (2H, q, J = 7.1 Hz), 5.30 (2H, s), 7.12 (4H, s), 8.25 (3H, brs), 8.56 (1H, s).

Example 173

2-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-1,3-thiazole-4-carboxylic acid dihydrochloride

1) 2-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-1,3-thiazole-4-carboxylic acid (1.21 g, yield 95%) was obtained as a colorless oil from [4-(ethoxycarbonyl)-1,3-thiazol-2-yl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.34 g, 2.30 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) δ:0.98 (6H, d, J = 6.4 Hz), 1.38 (9H, s), 2.16-2.28 (1H, m), 2.33 (3H, s), 2.61 (3H, brs), 2.85 (2H, brs), 4.11-4.19 (2H, m), 4.23 (1H, brs), 5.22 (2H, s), 7.02 (2H, d, J = 7.9 Hz), 7.10 (2H, d, J = 7.4 Hz), 8.24 (1H, s).

2) 2-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-1,3-thiazole-4-carboxylic acid dihydrochloride (362 mg, yield 83%) was obtained as a pale-yellow powder from 2-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-1,3-thiazole-4-carboxylic acid (460 mg, 0.831 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.96 (6H, d, J = 6.6 Hz), 2.16-2.27 (1H, m), 2.30 (3H, s), 2.53 (3H, s), 2.85 (2H, d, J = 7.0 Hz), 3.80 (2H, d, J = 5.1 Hz), 5.29 (2H, s), 7.12 (4H, s), 8.21 (3H, brs), 8.48 (1H, s).

Example 174

[4-(aminocarbonyl)-1,3-thiazol-2-yl]methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) [4-(Aminocarbonyl)-1,3-thiazol-2-yl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (420 mg, yield 70%) was obtained as a colorless oil from 2-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-1,3-thiazole-4-carboxylic acid (602 mg, 1.09 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.18-2.27 (1H, m), 2.33 (3H, s), 2.57 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 4.10-4.16 (2H, m), 4.22 (1H, brs), 5.17 (2H, s), 5.64 (1H, brs), 7.01 (2H, d, J = 7.9 Hz), 7.09 (2H, d, J = 7.9 Hz), 8.13 (1H, s).

2) [4-(Aminocarbonyl)-1,3-thiazol-2-yl]methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (208 mg, yield 48%) was obtained as a white powder from [4-(aminocarbonyl)-1,3-thiazol-2-yl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (460 mg, 0.832 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.96 (6H, d, J = 6.6 Hz), 2.18-2.27 (1H, m), 2.30 (3H, s), 2.53 (3H, s), 2.79-2.89 (2H, m), 3.79 (2H, d, J = 5.5 Hz), 5.28 (2H, s), 7.12 (4H, s), 7.62 (1H, brs), 7.66 (1H, brs), 8.22 (3H, brs), 8.48 (1H, s).

Example 175

[(2,2-dimethylpropanoyl)oxy]methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) To a solution (20 mL) of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.50 g, 3.37 mmol) in N,N-dimethylformamide were added chloromethyl pivalate (0.59 mL, 4.04 mmol) and potassium carbonate (0.93 g, 6.72 mmol) and the

mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give [(2,2-dimethylpropanoyl)oxy]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.68 g, yield 95%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.16 (9H, s), 1.39 (9H, s), 2.14-2.29 (1H, m), 2.38 (3H, s), 2.54 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 4.13 (2H, d, J = 4.9 Hz), 4.21 (1H, brs), 5.57 (2H, s), 7.06 (2H, d, J = 8.1 Hz), 7.20 (2H, d, J = 7.9 Hz).

2) [(2,2-Dimethylpropanoyl)oxy]methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (1.58 g , yield 99%) was obtained as a white solid from [(2,2-dimethylpropanoyl)oxy]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.68 g, 3.19 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) δ:0.96 (6H, d, J = 6.6 Hz), 1.09 (9H, s), 2.17-2.29 (1H, m), 2.37 (3H, s), 2.49 (3H, s), 2.84 (2H, d, J = 7.0 Hz), 3.78 (2H, d, J = 5.5 Hz), 5.61 (2H, s), 7.19 (2H, d, J = 8.1 Hz), 7.28 (2H, d, J = 8.1 Hz), 8.20 (3H, brs).

Example 176

(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) To a solution (20 mL) of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.50 g, 3.37 mmol) in N,N-dimethylformamide were added 4-(chloromethyl)-5-methyl-1,3-dioxol-2-one (0.60 g, 4.04 mmol) and potassium carbonate (0.93 g, 6.72 mmol) and the mixture was stirred at room temperature

for 1 hr. The reaction mixture was diluted with ethyl acetate (100 mL) and the mixture was washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.50 g, yield 85%) as a colorless il.

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8 Hz), 1.38 (9H, s), 1.97 (3H, s), 2.16-2.26 (1H, m), 2.40 (3H, s), 2.54 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 4.09 (2H, s), 4.74 (2H, s), 7.10 (2H, d, J = 7.9 Hz), 7.17 (2H, d, J = 7.9 Hz).

2) (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (1.21 g, yield 85%) was obtained as a white powder from (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.50 g, 2.86 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 1.97 (3H, s), 2.17-2.28 (1H, m), 2.35 (3H, s), 2.82 (2H, d, J = 7.0 Hz), 3.79 (2H, d, J = 5.5 Hz), 4.93 (2H, s), 7.12 (2H, d, J = 8.1 Hz), 7.20 (2H, d, J = 7.9 Hz), 8.15 (3H, brs).

Example 177

3-oxo-1,3-dihydro-2-benzofuran-1-yl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) To a solution (30 mL) of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.50 g, 3.37 mmol) in N,N-dimethylformamide were added 3-chloro-2-benzofuran-1(3H)-one (0.86 g, 4.04 mmol) and potassium carbonate (0.93 g, 6.72 mmol) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate (100 mL) and the mixture was washed with saturated brine. The organic layer

was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give 3-oxo-1,3-dihydro-2-benzofuran-1-yl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.83 g, yield 99%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.16-2.25 (1H, m), 2.42 (3H, s), 2.63 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 4.12 (2H, s), 6.98-7.08 (3H, m), 7.17 (2H, d, J = 7.9 Hz), 7.24 (1H, s), 7.59-7.64 (2H, m), 7.83-7.88 (1H, m).

2) 3-Oxo-1,3-dihydro-2-benzofuran-1-yl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride was obtained as a white powder from 3-oxo-1,3-dihydro-2-benzofuran-1-yl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.83 g, 3.36 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.95 (6H, d, J = 6.6 Hz), 2.15-2.28 (1H, m), 2.38 (3H, s), 2.59 (3H, s), 2.81 (2H, d, J = 7.2 Hz), 3.79 (2H, d, J = 5.7 Hz), 7.07-7.15 (3H, m), 7.25-7.32 (2H, m), 7.40 (1H, s), 7.73-7.75 (1H, m), 7.79-7.84 (1H, m), 7.89 (1H, d, J = 7.5 Hz), 8.12 (3H, brs).

Example 178

(2E)-2-(3-oxo-2-benzofuran-1(3H)-ylidene)ethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) To a solution (10 mL) of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (380 mg, 0.853 mmol) in N,N-dimethylformamide were added (3E)-3-(2-chloroethylidene)-2-benzofuran-1(3H)-one (170 mg, 0.711 mmol) and potassium carbonate (147 mg, 1.07 mmol) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate (100 mL) and the mixture was washed with

saturated brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give (2E)-2-(3-oxo-2-benzofuran-1(3H)-ylidene)ethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (270 mg, yield 55%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.16-2.26 (4H, m), 2.58 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 4.12 (2H, s), 4.21 (1H, brs), 4.85 (2H, d, J = 7.4 Hz), 5.25 (1H, t, J = 7.4 Hz), 7.07 (2H, d, J = 8.3 Hz), 7.12 (2H, d, J = 8.1 Hz), 7.55-7.64 (2H, m), 7.72-7.78 (1H, m), 7.92-7.95 (1H, m).

2) (2E)-2-(3-Oxo-2-benzofuran-1(3H)-ylidene)ethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (204 mg, yield 79%) was obtained as a white powder from (2E)-2-(3-oxo-2-benzofuran-1(3H)-ylidene)ethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (270 mg, 0.473 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.95 (6H, d, J = 6.6 Hz), 2.07 (3H, s), 2.18-2.29 (1H, m), 2.79 (2H, d, J = 6.6 Hz), 3.78 (2H, d, J = 7.4 Hz), 4.81 (2H, d, J = 7.5 Hz), 5.68 (1H, t, J = 7.5 Hz), 7.14 (4H, s), 7.71-7.77 (1H, m), 7.90-8.00 (3H, m), 8.06 (3H, brs).

Example 179

benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate

To a solution (30 mL) of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (3.00 g, 6.73 mmol) in N,N-dimethylformamide were added benzyl bromide (0.80 mL, 6.73 mmol) and potassium carbonate (1.85 g, 13.4 mmol) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate (200 mL) and the mixture

was washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was dissolved in trifluoroacetic acid (50 mL) and the mixture was stirred at room temperature for 3 hrs. Trifluoroacetic acid was evaporated under reduced pressure, and the residue was neutralized with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (2.70 g, yield 99%) as a yellow solid.

^{1}H-NMR ($CDCl_3$) :0.91 (6H, d, J = 6.6 Hz), 2.07-2.18 (1H, m), 2.34 (3H, s), 2.51 (3H, s), 2.72 (2H, d, J = 7.4 Hz), 3.84 (2H, s), 4.94 (2H, s), 7.02-7.12 (6H, m), 7.24-7.31 (3H, m).

Example 180

2-oxo-1,3-dioxolan-4-yl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) To a solution (30 mL) of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.50 g, 3.37 mmol) in N,N-dimethylformamide were added 4-chloro-1,3-dioxolan-2-one (0.55 g, 4.04 mmol) and potassium carbonate (0.70 g, 5.05 mmol) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate (100 mL) and the mixture was washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give 2-oxo-1,3-dioxolan-4-yl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.39 g, yield 83%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.19-2.28 (1H, m), 2.41 (3H, s), 2.60 (3H, s), 2.81 (2H, d, J = 7.4 Hz), 3.67 (1H, dd, J = 10.2, 1.5 Hz), 4.16 (2H, d, J = 4.9 Hz), 4.22 (1H, brs), 4.31 (1H, dd, J = 10.0, 5.7 Hz), 4.63-4.82 (1H, m), 6.41-6.46 (1H, m), 7.01-7.10 (2H, m), 7.19-7.26 (2H, m).

2) 2-Oxo-1,3-dioxolan-4-yl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (1.31 g, yield 99%) was obtained as a white powder from 2-oxo-1,3-dioxolan-4-yl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.39 g, 2.79 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.18-2.28 (1H, m), 2.36 (3H, s), 2.55 (3H, s), 2.85 (2H, d, J = 7.0 Hz), 3.83 (2H, d, J = 5.7 Hz), 4.04 (1H, dd, J = 10.2, 1.7 Hz), 4.59 (1H, dd, J = 10.1, 5.7 Hz), 6.59 (1H, dd, J = 5.4 Hz), 7.14-7.20 (2H, m), 7.24-7.29 (2H, m), 8.23 (3H, brs).

Example 181

5-(aminomethyl)-4-(4-hydroxyphenyl)-6-isobutyl-2-methylnicotinic acid dihydrochloride

1) tert-Butyl 4-[4-(benzyloxy)phenyl]-5-cyano-6-isobutyl-2-methyl-1,4-dihydropyridine-3-carboxylate (21.4 g, yield 77%) was obtained as pale-pink solid from 4-(benzyloxy)benzaldehyde (12.8 g, 60.4 mmol) according to a method similar to the method of Example 1-2).

^{1}H-NMR ($CDCl_3$) :0.94 (3H, d, J = 6.6 Hz), 0.99 (3H, d, J = 6.6 Hz), 1.28 (9H, s), 1.80-1.96 (1H, m), 2.14-2.29 (2H, m), 2.32 (3H, s), 4.51 (1H, s), 5.03 (2H, s), 5.49 (1H, s), 6.90 (2H, d, J = 8.7 Hz), 7.15 (2H, d, J = 8.7 Hz), 7.29-7.46 (5H, m).

2) tert-Butyl 4-[4-(benzyloxy)phenyl]-5-cyano-6-isobutyl-2-methylnicotinate (2.18 g, yield 94%) was obtained as a yellow solid from tert-butyl 4-[4-(benzyloxy)phenyl]-5-cyano-6-isobutyl-2-methyl-1,4-dihydropyridine-3-carboxylate (2.33 g, 5.08 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) :1.01 (6H, d, J = 6.6 Hz), 1.25 (9H, s), 2.17-2.33 (1H, m), 2.63 (3H, s), 2.93 (2H, d, J = 7.4 Hz), 5.12 (2H, s), 7.06 (2H, d, J = 8.9 Hz), 7.31 (2H, d, J = 8.9 Hz), 7.39-7.49 (5H, m).

3) tert-Butyl 5-(aminomethyl)-4-(4-hydroxyphenyl)-6-isobutyl-2-methylnicotinate was obtained as a crude product from tert-butyl 4-[4-(benzyloxy)phenyl]-5-cyano-6-isobutyl-2-methylnicotinate (2.13 g, 4.67 mmol) according to a method similar to the method of Example 1-4). tert-Butyl 5-{[(tert-butoxycarbonyl)amino]methyl}-4-(4-hydroxyphenyl)-6-isobutyl-2-methylnicotinate (1.35 g, yield 61%) was obtained as a pale-yellow solid from the crude product according to a method similar to the method of Example 2-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.22 (9H, s), 1.40 (9H, s), 2.12-2.27 (1H, m), 2.55 (3H, s), 2.76 (2H, d, J = 7.2 Hz), 4.14 (2H, d, J = 4.9 Hz), 4.25 (1H, brs), 5.50 (1H, brs), 6.85 (2H, d, J = 8.5 Hz), 7.07 (2H, d, J = 8.5 Hz).

4) tert-Butyl 5-{[(tert-butoxycarbonyl)amino]methyl}-4-(4-hydroxyphenyl)-6-isobutyl-2-methylnicotinate (316 mg, 0.671 mmol) and anisole (218 mg, 2.01 mmol) were dissolved in trifluoroacetic acid (5 mL) and the mixture was stirred at room temperature for 5 hrs. Trifluoroacetic acid was evaporated under reduced pressure and 4N hydrogen chloride 1,4-dioxane solution (20 mL) was added to the residue. The mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the obtained yellow solid was washed with diisopropyl ether to give 5-(aminomethyl)-4-(4-hydroxyphenyl)-6-isobutyl-2-methylnicotinic acid dihydrochloride (259 mg, yield 99%) as a yellow powder.

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 2.14-2.27 (1H, m), 2.59 (3H, s), 2.92 (2H, d, J = 5.7 Hz), 3.86 (2H, d, J = 4.9 Hz), 6.87 (2H, d, J = 8.5 Hz), 7.14 (2H, d, J = 8.3 Hz), 8.26 (3H, brs).

Example 182

5-(aminomethyl)-6-isobutyl-4-(4-methoxyphenyl)-2-methylnicotinic acid dihydrochloride

1) To a solution (20 mL) of tert-butyl 5-{[(tert-butoxycarbonyl)amino]methyl}-4-(4-hydroxyphenyl)-6-isobutyl-2-methylnicotinate (620 mg, 1.32 mmol) and potassium carbonate (365 mg, 2.64 mmol) in N,N-dimethylformamide was added iodomethane (374 mg, 2.64 mmol) and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate (100 mL) and the mixture was washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give tert-butyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methoxyphenyl)-2-methylnicotinate (520 mg, yield 81%) as a colorless oil .

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8 Hz), 1.21 (9H, s), 1.39 (9H, s), 2.13-2.26 (1H, m), 2.55 (3H, s), 2.76 (2H, d, J = 7.4 Hz), 3.84 (3H, s), 4.12 (2H, s), 4.22 (1H, brs), 6.94 (2H, d, J = 8.7 Hz), 7.12 (2H, d, J = 8.7 Hz).

2) 5-(Aminomethyl)-6-isobutyl-4-(4-methoxyphenyl)-2-methylnicotinic acid dihydrochloride (429 mg, yield 99%) was obtained as a yellow powder from tert-butyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methoxyphenyl)-2-methylnicotinate (520 mg, 1.07 mmol) according to a method similar to the method of Example 181-4).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 2.16-2.27 (1H, m), 2.54 (3H, s), 2.85 (2H, d, J = 6.6 Hz), 3.57(3H, s), 3.84 (2H, s), 7.05 (2H, d, J = 8.7 Hz), 7.26 (2H, d, J = 8.7 Hz), 8.17 (3H, brs).

Example 183

methyl 4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate dihydrochloride

1) A mixture of tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.00 g,

2.51 mmol), triethylamine (0.7 mL, 5.02 mmol) and tetrahydrofuran (20 mL) was cooled to 0 C and methanesulfonyl chloride (432 mg, 3.77 mmol) was added dropwise. After stirring at room temperature for 30 min., the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to give [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl methanesulfonate as a crude product. The crude product was dissolved in N,N-dimethylformamide (15 mL), and potassium carbonate (520 mg, 3.77 mmol) and methyl 4-mercaptobenzoate (422 mg, 2.51 mmol) were added. The mixture was stirred with heating at 50 C for 1 hr. The reaction mixture was diluted with ethyl acetate (100 mL) and the mixture was washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give methyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate (1.01 g, yield 73%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.16-2.25 (1H, m), 2.37 (3H, s), 2.65 (3H, s), 2.75 (2H, d, J = 7.4 Hz), 3.86 (2H, s), 3.89 (3H, s), 4.04 (2H, d, J = 5.1 Hz), 4.20 (1H, brs), 7.04 (2H, d, J = 7.9 Hz), 7.09 (2H, d, J = 8.7 Hz), 7.19 (2H, d, J = 7.7 Hz), 7.85 (2H, d, J = 8.7 Hz).

2) Methyl 4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate dihydrochloride (138 mg, yield 73%) was obtained as a pale-yellow powder from methyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate (200 mg, 0.365 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.12-2.23 (1H, m), 2.35 (3H, s), 2.81 (3H, s), 3.64 (2H, brs), 3.75 (2H, d, J = 5.7 Hz), 3.83 (3H, s), 4.01 (2H, s), 7.24-7.33 (6H, m), 7.82 (2H, d, J = 8.7 Hz), 8.30 (3H, brs).

Example 184

4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoic acid dihydrochloride

1) 4-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoic acid (0.97 g, yield 72%) was obtained as a white solid from methyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate (1.37 g, 2.51 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :1.07 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.23-2.35 (1H, m), 2.42 (3H, s), 3.08 (3H, s), 3.30-3.40 (2H, m), 3.90 (2H, s), 4.12-4.18 (2H, m), 4.30 (1H, brs), 7.05 (2H, d, J = 7.9 Hz), 7.13 (2H, d, J = 8.5 Hz), 7.23-7.31 (2H, m), 7.93 (2H, d, J = 8.5 Hz).

2) 4-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoic acid dihydrochloride (198 mg, yield 77%) was obtained as a white powder from 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoic acid (0.27 g, 0.505 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.13-2.23 (1H, m), 2.36 (3H, s), 2.81 (3H, s), 3.05 (2H, brs), 3.71-3.80 (2H, m), 4.01 (2H, s), 7.23-7.27 (4H, m), 7.32 (2H, d, J = 8.1 Hz), 7.80 (2H, d, J = 8.3 Hz), 8.32 (3H, brs).

Example 185

methyl 4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}sulfonyl)benzoate

dihydrochloride

1) Methyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}sulfonyl)benzoate (410 mg, yield 84%) was obtained as a colorless oil from methyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate (0.46 g, 0.838 mmol) according to a method similar to the method of Example 91-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.7 Hz), 1.38 (9H, s), 2.17-2.26 (1H, m), 2.41 (3H, s), 2.64 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.98 (3H, s), 4.00 (2H, d, J = 5.3 Hz), 4.18 (1H, brs), 4.32 (2H, s), 6.87 (2H, d, J = 7.7 Hz), 7.17 (2H, d, J = 7.7 Hz), 7.56 (2H, d, J = 8.5 Hz), 8.08 (2H, d, J = 8.5 Hz).

2) Methyl 4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}sulfonyl)benzoate dihydrochloride (352 mg, yield 90%) was obtained as a pale-yellow powder from methyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}sulfonyl)benzoate (410 mg, 0.706 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.17-2.27 (1H, m), 2.38 (3H, s), 2.78 (3H, s), 3.00 (2H, brs), 3.66-3.74 (2H, m), 3.93 (3H, s), 4.61 (2H, brs), 7.05 (2H, d, J = 7.9 Hz), 7.23 (2H, d, J = 7.9 Hz), 7.66 (2H, d, J = 8.3 Hz), 8.09 (2H, d, J = 8.7 Hz), 8.30 (3H, brs).

Example 186

4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}sulfonyl)benzoic acid dihydrochloride

1) 4-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}sulfonyl)benzoic acid (300 mg, yield 93%) was obtained as a colorless oil from

methyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}sulfonyl)benzoate (330 mg, 0.568 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.14-2.22 (1H, m), 2.34 (3H, s), 2.43 (3H, s), 2.86 (2H, d, J = 7.4 Hz), 4.06 (2H, d, J = 4.5 Hz), 4.28 (1H, brs), 4.35 (2H, s), 6.97 (2H, d, J = 7.9 Hz), 7.23 (2H, d, J = 7.7 Hz), 7.60 (2H, d, J = 8.1 Hz), 8.17 (2H, d, J = 8.1 Hz).

2) 4-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}sulfonyl)benzoic acid dihydrochloride (279 mg, yield 97%) was obtained as a white powder from 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}sulfonyl)benzoic acid (300 mg, 0.530 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 2.17-2.24 (1H, m), 2.38 (3H, s), 2.76 (3H, brs), 2.95 (2H, brs), 3.70 (2H, brs), 7.05 (2H, d, J = 7.9 Hz), 7.23 (2H, d, J = 7.9 Hz), 7.62 (2H, d, J = 8.3 Hz), 8.07 (2H, d, J = 8.3 Hz), 8.24 (3H, brs).

Example 187

N-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}methanesulfonamide dihydrochloride

1) To a solution (10 mL) of tert-butyl {[5-(aminomethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (200 mg, 0.755 mmol) and triethylamine (0.14 mL, 1.00 mmol) in tetrahydrofuran was added methanesulfonyl chloride (86 mg, 0.875 mmol) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate (100 mL) and washed successively with saturated aqueous sodium hydrogen carbonate and saturated brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and

the obtained yellow solid was washed with diisopropyl ether to give tert-butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[(methylsulfonyl)amino]methyl}pyridin-3-yl)methyl]carbamate (210 mg, yield 87%) as a white solid.

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.16-2.25 (1H, m), 2.42 (3H, s), 2.61 (3H, s), 2.68 (3H, s), 2.76 (2H, d, J = 7.4 Hz), 3.87 (1H, brs), 4.01 (2H, d, J = 5.7 Hz), 4.03 (2H, d, J = 5.3 Hz), 4.18 (1H, brs), 7.03 (2H, d, J = 8.1 Hz), 7.29 (2H, d, J = 7.9 Hz).

2) N-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}methanesulfonamide dihydrochloride (126 mg, yield 64%) was obtained as a white powder from tert-butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[(methylsulfonyl)amino]methyl}pyridin-3-yl)methyl]carbamate (210 mg, 0.441 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.12-2.23 (1H, m), 2.41 (3H, s), 2.71 (3H, s), 2.84 (3H, brs), 3.04 (2H, brs), 3.76 (2H, brs), 3.87 (2H, brs), 7.19 (1H, brs), 7.29 (2H, d, J = 7.5 Hz), 7.38 (2H, d, J = 7.7 Hz), 8.28 (3H, brs).

Example 188

{[4-(2,4-dichlorophenyl)-6-(4-fluorophenyl)-2-isobutylpyridin-3-yl]methyl}amine dihydrochloride

1) (2E)-3-(2,4-Dichlorophenyl)-1-(4-fluorophenyl)prop-2-en-1-one (10.3 g, yield 64%) was obtained as a pale-yellow solid from 4-fluoroacetophenone (6.91 g, 50 mmol) and 2,6-dichlorobenzamide (8.75 g, 59 mmol) according to a method similar to the method of Example 108-1).

^{1}H-NMR ($CDCl_3$) : 7.16-7.23 (2H, m), 7.31 (1H, dd, J = 8.5, 2.1 Hz), 7.42-7.49 (2H, m), 7.68 (2H, d, J = 8.5 Hz), 8.07 (3H, m).

2) 4-(2,4-Dichlorophenyl)-6-(4-fluorophenyl)-2-isobutylnicotinonitrile (2.94 g, yield 48%) was obtained as a yellow oil from (2E)-3-(2,4-dichlorophenyl)-1-(4-fluorophenyl)prop-2-en-1-one (4.54 g, 15.4 mmol) according to a

method similar to the method of Example 108-2).

^{1}H-NMR ($CDCl_3$) :1.06 (6H, d, J = 6.6 Hz), 2.32-2.45 (1H, m), 3.04 (2H, d, J = 7.2 Hz), 7.09-7.24 (3H, m), 7.33 (1H, d, J = 8.3 Hz), 7.37-7.44 (1H, m), 7.57 (1H, s), 7.59 (1H, d, J = 1.9 Hz), 8.06-8.12 (1H, m).

3) {[4-(2,4-Dichlorophenyl)-6-(4-fluorophenyl)-2-isobutylpyridin-3-yl]methyl}amine (780 mg, yield 68%) was obtained as a pale-yellow oil from 4-(2,4-dichlorophenyl)-6-(4-fluorophenyl)-2-isobutylnicotinonitrile (1.14 g, 2.85 mmol) according to a method similar to the method of Example 23-4). The oil was dissolved in 4N hydrogen chloride 1,4-dioxane solution (20 mL) and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the obtained pale-yellow solid was washed with diisopropyl ether to give {[4-(2,4-dichlorophenyl)-6-(4-fluorophenyl)-2-isobutylpyridin-3-yl]methyl}amine dihydrochloride (895 mg, yield 97%) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6) :0.97 (3H, d, J = 6.6 Hz), 1.05 (3H, d, J = 6.6 Hz), 2.29-2.38 (1H, m), 2.81-2.99 (2H, m), 3.57-3.64 (1H, m), 4.04-4.16 (1H, m), 7.33 (2H, t, J = 8.8 Hz), 7.59-7.67 (2H, m), 7.73 (1H, s), 7.86 (1H, d, J = 1.9 Hz), 8.21-8.30 (5H, m).

Example 189

methyl 3-[5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate dihydrochloride

1) (2E)-1-(3-Bromophenyl)-3-(4-methylphenyl)prop-2-en-1-one (7.09 g, yield 47%) was obtained as a pale-yellow powder from 3-bromoacetophenone (9.95 g, 50 mmol) according to a method similar to the method of Example 108-1).

2) 6-(3-Bromophenyl)-2-isobutyl-4-(4-methylphenyl)nicotinonitrile (2.20 g, yield 32%) was obtained as a pale-yellow solid from (2E)-1-(3-bromophenyl)-3-(4-methylphenyl)prop-2-en-1-one (5.03 g, 16.7 mmol) according to a method similar to the method of Example 108-2).

^{1}H-NMR ($CDCl_3$) :1.06 (6H, d, J = 6.6 Hz), 2.35-2.42 (1H, m),

2.45 (3H, s), 3.06 (2H, d, J = 7.4 Hz), 7.09-7.16 (3H, m), 7.30-7.40 (4H, m), 7.53-7.55 (1H, m), 7.64 (1H, s).

3) 6-(3-Bromophenyl)-2-isobutyl-4-(4-methylphenyl)nicotinonitrile (2.20 g, 5.40 mmol), triethylamine (0.70 mL, 10.0 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (410 mg, 0.500 mmol) were dissolved in a mixed solvent of methanol (10 mL)-N,N-dimethylformamide (30 mL) and the mixture was stirred under a carbon monoxide atmosphere for 15 hrs. The reaction mixture was diluted with ethyl acetate (100 mL) and the mixture was washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give methyl 3-[5-cyano-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate (1.39 g, yield 72%) as a colorless oil. Methyl 3-[5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate (780 mg, yield 58%) was obtained as a colorless oil from methyl 3-[5-cyano-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate (1.30 g, 3.38 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) :1.05 (6H, d, J = 6.6 Hz), 2.37-2.48 (4H, m), 2.90 (2H, d, J = 7.2 Hz), 3.84 (2H, s), 3.94 (3H, s), 7.27-7.33 (4H, m), 7.49 (1H, s), 7.54 (1H, t, J = 7.9 Hz), 8.04-8.07 (1H, m), 8.32 (1H, m), 8.61-8.62 (1H, m).

4) Methyl 3-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate (730 mg, yield 76%) was obtained as a white powder from methyl 3-[5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate (0.76 g, 1.96 mmol) according to a method similar to the method of Example 2-1).

^{1}H-NMR ($CDCl_3$) :1.04 (6H, d, J = 6.6 Hz), 1.43 (9H, s), 2.37-2.46 (4H, m), 2.87 (2H, d, J = 7.2 Hz), 3.94 (3H, s), 4.29-4.35 (2H, m), 4.38 (1H, brs), 7.23 (2H, d, J = 8.3 Hz), 7.28 (2H, d,

J = 8.1 Hz), 7.50 (1H, s), 7.54 (1H, t, J = 7.8 Hz), 8.05-8.08 (1H, m), 8.30-8.34 (1H, m), 8.62-8.63 (1H, m).

5) Methyl 3-[5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate dihydrochloride (188 mg, yield 99%) was obtained as a white powder from methyl 3-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate (200 mg, 0.409 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.04 (6H, d, J = 6.4 Hz), 2.33-2.44 (4H, m), 2.93 (2H, d, J = 7.0 Hz), 3.90 (3H, s), 4.01 (2H, d, J = 5.5 Hz), 7.36 (2H, d, J = 8.1 Hz), 7.41 (2H, d, J = 8.3 Hz), 7.66 (1H, t, J = 7.8 Hz), 7.76 (1H, s), 8.01-8.08 (1H, m), 8.40 (3H, brs), 8.42-8.47 (1H, m), 8.71-8.75 (1H, m).

Example 190

3-[5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoic acid dihydrochloride

1) 3-[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoic acid (500 mg, yield 98%) was obtained as a white solid from methyl 3-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate (530 mg, 1.08 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :1.05 (6H, d, J = 6.6 Hz), 1,43 (9H, s), 2.35-2.47 (4H, m), 2.92 (2H, brs), 4.31-4.37 (2H, m), 4.42 (1H, brs), 7.22-7.30 (4H, m), 7.52 (1H, s), 7.58 (1H, t, J = 7.5 Hz), 8.12 (1H, d, J = 7.9 Hz), 8.36 (1H, d, J = 7.4 Hz), 8.67 (1H, s).

2) 3-[5-(Aminomethyl)-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoic acid dihydrochloride (188 mg, yield 99%) was obtained as a white powder from 3-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoic acid (200 mg, 0.421 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.03 (6H, d, J = 7.4 Hz), 2.32-2.43 (4H, m),

2.92 (2H, d, J = 7.0 Hz), 4.02 (2H, d, J = 5.3 Hz), 7.36 (2H, d, J = 8.1 Hz), 7.41 (2H, d, J = 8.3 Hz), 7.63 (1H, t, J = 7.8 Hz), 7.74 (1H, s), 8.01-8.04 (1H, m), 8.35 (3H, brs), 8.37-8.41 (1H, m), 8.71-8.72 (1H, m).

Example 191

3-[5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzamide dihydrochloride

1) tert-Butyl {[6-[3-(aminocarbonyl)phenyl]-2-isobutyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (160 mg, yield 53%) was obtained as a white solid from 3-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoic acid (300 mg, 0.632 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :1.04 (6H, d, J = 6.6 Hz), 1,43 (9H, s), 2.34-2.48 (4H, m), 2.87 (2H, d, J = 7.2 Hz), 4.32 (2H, d, J = 4.7 Hz), 4.39 (1H, brs), 7.22 (2H, d, J = 8.1 Hz), 7.25-7.29 (2H, m), 7.50 (1H, s), 7.55 (1H, t, J = 7.8 Hz), 7.83-7.87 (1H, m), 8.21-8.25 (1H, m), 8.45-8.46 (1H, m).

2) 3-[5-(Aminomethyl)-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzamide dihydrochloride (127 mg, yield 84%) was obtained as a white powder from tert-butyl {[6-[3-(aminocarbonyl)phenyl]-2-isobutyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (160 mg, 0.338 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.03 (6H, d, J = 6.6 Hz), 2.34-2.44 (4H, m), 2.93 (2H, d, J = 7.0 Hz), 4.01 (2H, d, J = 5.5 Hz), 7.37 (2H, d, J = 8.1 Hz), 7.42 (2H, d, J = 8.1 Hz), 7.47 (1H, brs), 7.60 (1H, t, J = 7.8 Hz), 7.81 (1H, s), 7.96 (1H, d, J = 7.7 Hz), 8.14 (1H, brs), 8.33-8.44 (4H, m), 8.58 (1H, s).

Example 192

methyl 2-[5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate dihydrochloride

1) (2E)-1-(2-Bromophenyl)-3-(4-methylphenyl)prop-2-en-1-one (8.86 g, yield 44%) was obtained as a pale-yellow powder from

2-bromoacetophenone (9.95 g, 50 mmol) according to a method similar to the method of Example 108-1).

2) 6-(2-Bromophenyl)-2-isobutyl-4-(4-methylphenyl)nicotinonitrile (3.58 g, yield 53%) was obtained as a pale-yellow solid from (2E)-1-(2-bromophenyl)-3-(4-methylphenyl)prop-2-en-1-one (5.03 g, 16.7 mmol) according to a method similar to the method of Example 108-2).

^{1}H-NMR ($CDCl_3$) :1.06 (6H, d, J = 6.6 Hz), 2.34-2.44 (4H, m), 3.07 (2H, d, J = 7.4 Hz), 7.27-7.30 (1H, m), 7.32-7.36 (2H, m), 7.41-7.47 (1H, m), 7.53-7.60 (3H, m), 7.71 (1H, m).

3) Methyl 2-[5-cyano-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate (1.80 g, yield 76%) was obtained as a colorless oil from 6-(2-bromophenyl)-2-isobutyl-4-(4-methylphenyl)nicotinonitrile (2.50 g, 6.14 mmol) according to a method similar to the method of Example 189-3). That is, 6-(2-bromophenyl)-2-isobutyl-4-(4-methylphenyl)nicotinonitrile, triethylamine (1.7 mL, 12.2 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (501 mg, 0.614 mmol) were dissolved in methanol (7.5 mL) - N,N-dimethylformamide (15 mL) and the mixture was stirred under a carbon monoxide atmosphere for 13 hrs. The reaction mixture was diluted with ethyl acetate (100 mL) and the mixture was washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give methyl 2-[5-cyano-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate.

^{1}H-NMR ($CDCl_3$) :1.03 (6H, d, J = 6.8 Hz), 2.26-2.37 (1H, m), 2.44 (3H, s), 3.01 (2H, d, J = 7.4 Hz), 3.74 (3H, s), 7.08-7.14 (1H, m), 7.34 (2H, d, J = 7.9 Hz), 7.42 (1H, s), 7.48-7.61 (4H, m), 7.83-7.88 (1H, m).

4) Methyl 2-[5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate was obtained as a crude product from methyl 2-[5-cyano-6-isobutyl-4-(4-

methylphenyl)pyridin-2-yl]benzoate (1.80 g, 4.68 mmol) according to a method similar to the method of Example 1-4). Methyl 2-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate (1.70 g, yield 74%) was obtained as a colorless oil from the crude product according to a method similar to the method of Example 2-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.43 (9H, s), 2.26-2.37 (1H, m), 2.41 (3H, s), 2.80 (2H, d, J = 7.4 Hz), 3.75 (3H, s), 4.32 (2H, d, J = 4.9 Hz), 4.42 (1H, brs), 7.21-7.27 (5H, m), 7.41-7.46 (1H, m), 7.52-7.58 (2H, m), 7.76 (1H, dd, J = 7.4, 1.1 Hz).

5) Methyl 2-[5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate dihydrochloride (345 mg, yield 95%) was obtained as a pale-pink powder from methyl 2-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate (383 mg, 0.786 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 2.18-2.32 (1H, m), 2.41 (3H, s), 2.89 (2H, d, J = 6.6 Hz), 3.69 (3H, s), 3.99-4.09 (2H, m), 7.36 (2H, d, J = 8.1 Hz), 7.43 (2H, d, J = 8.1 Hz), 7.49 (1H, s), 7.57-7.70 (2H, m), 7.76 (2H, d, J = 7.5 Hz), 8.51 (3H, brs).

Example 193

2-[5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoic acid dihydrochloride

1) 2-[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoic acid (0.85 g, yield 67%) was obtained as a colorless oil from methyl 2-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoate (1.31 g, 2.69 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :1.02 (6H, d, J = 6.6 Hz), 1.42 (9H, s), 2.21-2.33 (1H, m), 2.44 (3H, s), 2.93 (2H, d, J = 7.4 Hz), 4.39 (2H, brs), 7.22 (2H, d, J = 8.1 Hz), 7.31 (2H, d, J = 7.9 Hz), 7.48

(1H, s), 7.54-7.66 (3H, m), 8.31 (1H, m).

2) 2-[5-(Aminomethyl)-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoic acid dihydrochloride (329 mg, yield 81%) was obtained as a white powder from 2-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoic acid (429 mg, 0.904 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.27-2.36 (1H, m), 2.41 (3H, s), 2.90 (2H, d, J = 6.6 Hz), 4.04 (2H, d, J = 5.1 Hz), 7.36 (2H, d, J = 8.3 Hz), 7.40-7.49 (3H, m), 7.54-7.70 (3H, m), 7.76-7.84 (1H, m), 8.44 (3H, brs).

Example 194

2-[5-(aminomethyl)-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzamide dihydrochloride

1) tert-Butyl {[6-[2-(aminocarbonyl)phenyl]-2-isobutyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (290 mg, yield 69%) was obtained as a colorless oil from 2-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzoic acid (421 mg, 0.887 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :1.01 (6H, d, J = 6.6 Hz), 1.43 (9H, s), 2.30-2.37 (1H, m), 2.41 (3H, s), 2.83 (2H, d, J = 7.4 Hz), 4.34 (2H, d, J = 4.7 Hz), 4.42 (1H, brs), 5.54 (1H, brs), 6.42 (1H, brs), 7.20 (2H, d, J = 8.3 Hz), 7.24-7.25 (3H, m), 7.42-7.53 (3H, m), 7.70-7.75 (1H, m).

2) 2-[5-(Aminomethyl)-6-isobutyl-4-(4-methylphenyl)pyridin-2-yl]benzamide dihydrochloride (254 mg, yield 93%) was obtained as a yellow powder from tert-butyl {[6-[2-(aminocarbonyl)phenyl]-2-isobutyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (290 mg, 0.612 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.01 (6H, d, J = 6.6 Hz), 2.27-2.37 (1H, m), 2.40 (3H, s), 2.90-2.99 (2H, m), 4.04 (2H, m), 7.36 (2H, d, J = 8.1 Hz), 7.41 (2H, d, J = 8.3 Hz), 7.50 (1H, s), 7.56-7.71 (4H,

m), 7.92-8.01 (1H, m), 8.61 (3H, brs).

Example 195

5-(aminomethyl)-N,N-dicyclohexyl-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinamide dihydrochloride

1) 5-Cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (2.16 g, yield 85%) was obtained as a white powder from tert-butyl 5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (3.00 g, 8.23 mmol) according to a method similar to the method of Example 24-1).

^{1}H-NMR ($CDCl_3$) :1.00 (6H, d, J = 6.6 Hz), 2.17-2.32 (1H, m), 2.42 (3H, s), 2.67 (3H, s), 2.95 (2H, d, J = 7.4 Hz), 7.27-7.34 (4H, m).

2) To a solution of 5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (2.00 g, 6.49 mmol) in dichloromethane were added oxalyl chloride (0.68 mL, 7.78 mmol) and N,N-dimethylformamide (0.05 mL) and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran. Subsequently, triethylamine (1.8 mL, 13.0 mmol) and dicyclohexylamine (1.55 mL, 7.78 mmol) were added and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give 5-cyano-N,N-dicyclohexyl-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinamide (0.35 g, yield 11%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) :0.79-0.96 (4H, m), 1.01 (6H, dd, J = 11.1, 6.6 Hz), 1.07-1.34 (4H, m), 1.40-1.53 (5H, m), 1.58-1.68 (4H, m), 1.72-1.84 (3H, m), 2.22-2.31 (1H, m), 2.40 (3H, s), 2.59 (3H, s), 2.69-2.79 (2H, m), 2.87-3.04 (2H, m), 7.25 (2H, d, J = 8.5 Hz), 7.46 (2H, d, J = 8.1 Hz).

3) 5-(Aminomethyl)-N,N-dicyclohexyl-6-isobutyl-2-methyl-4-(4-

methylphenyl)nicotinamide dihydrochloride (0.20 g, yield 49%) was obtained as a yellow powder from 5-cyano-N,N-dicyclohexyl-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinamide (0.35 g, 0.742 mmol) according to a method similar to the method of Example 108-3).

^{1}H-NMR (DMSO-d_6) :0.73-0.88 (2H, m), 0.90-1.15 (12H, m), 1.24-1.75 (10H, m), 2.13-2.27 (3H, m), 2.36 (3H, s), 2.78-2.86 (2H, m), 2.88-2.95 (2H, m), 3.68-3.81 (1H, m), 3.96-4.09 (1H, m), 7.26-7.37 (4H, m).

Example 196

methyl 1-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}piperidine-4-carboxylate dihydrochloride

1) Methyl 1-{[5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}piperidine-4-carboxylate (3.20 g, yield 91%) was obtained as a colorless oil from 5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (2.50 g, 8.1 mmol) and methyl isonipecotate (1.3 mL, 9.73 mmol) according to a method similar to the method of Example 195-2).

^{1}H-NMR ($CDCl_3$) :1.01 (6H, dd, J = 12.1, 6.6 Hz), 1.42-1.85 (4H, m), 2.19-2.37 (3H, m), 2.40 (3H, s), 2.55-2.60 (3H, m), 2.61-3.20 (5H, m), 3.63-3.66 (3H, m), 4.23-4.45 (1H, m), 7.25-7.42 (4H, m).

2) Methyl 1-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}piperidine-4-carboxylate dihydrochloride (3.27 g, yield 87%) was obtained as a white powder from methyl 1-{[5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}piperidine-4-carboxylate (3.20 g, 7.38 mmol) according to a method similar to the method of Example 108-3).

^{1}H-NMR (DMSO-d_6) :0.67-0.90 (1H, m), 0.98 (6H, t, J = 5.9 Hz), 1.25-1.76 (3H, m), 2.16-2.28 (1H, m), 2.36-2.37 (3H, m), 2.63-2.76 (1H, m), 2.90-3.03 (2H, m), 3.17-3.34 (1H, m), 3.57 (3H, s), 3.58-3.60 (2H, m), 3.68-3.97 (2H, m), 4.05-4.10 (1H, m),

7.11-7.36 (4H, m), 8.34 (3H, brs).

Example 197

5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid tert-butylamine salt

5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.10 g, 0.320 mmol) was dissolved in a mixed solvent of water (1.5 mL)-acetonitrile (1.5 mL) with heating under reflux for 10 min. tert-Butylamine (23.4 mg, 0.320 mmol) was added to the obtained solution and the mixture was stirred at the same temperature for 10 min. Acetonitrile (20 mL) was added, and the mixture was allowed to cool to room temperature and stirred at 0 C for 30 min. The precipitated solid was collected by filtration and washed with acetonitrile (10 mL) to give 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid tert-butylamine salt (78.4 mg, yield 63%) as a white powder.

^{1}H-NMR (DMSO-d_6) :0.91 (6H, d, J = 6.6 Hz), 1.12 (9H, s), 2.06-2.25 (1H, m), 2.31 (3H, s), 2.34 (3H, s), 2.66 (2H, d, J = 7.0 Hz), 3.31 (2H, brs), 3.37 (2H, s), 7.10 (2H, d, J = 8.1 Hz), 7.16 (2H, d, J = 8.1 Hz).

Example 198

({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(methylthio)methyl]pyridin-3-yl}methyl)amine dihydrochloride

1) To a solution of [5-({[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl methanesulfonate (476 mg, 1 mmol) in tetrahydrofuran (5 mL) was added 15% aqueous sodium methanethiolate solution (3 mL) and the mixture was stirred at 50 C for 2 hrs. 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. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give tert-butyl ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-

[(methylthio)methyl]pyridin-3-yl}methyl)carbamate (312 mg, yield 72%) as a white powder.

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 1.94 (3H, s), 2.12-2.23 (1H, m), 2.42 (3H, s), 2.67 (3H, s), 2.75 (2H, d, J = 6.9 Hz), 3.39 (2H, s), 4.02 (2H, d, J = 5.7 Hz), 4.19 (1H, brs), 7.04 (2H, d, J = 8.1 Hz), 7.24 (2H, d, J = 8.1 Hz).

2) ({2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-[(methylthio)methyl]pyridin-3-yl}methyl)amine dihydrochloride (36 mg, yield 96%) was obtained as a white powder from tert-butyl ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(methylthio)methyl]pyridin-3-yl}methyl)carbamate according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 1.93 (3H, s), 2.12-2.19(1H, m), 2.42 (3H, s), 2.89 (3H, s), 3.08 (2H, brs), 3.48 (2H, s), 3.75 (2H, s), 7.28 (2H, d, J = 7.8 Hz), 7.39 (2H, d, J = 7.8 Hz), 8.36 (3H, brs).

Example 199

({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(methylsulfonyl)methyl]pyridin-3-yl}methyl)amine dihydrochloride

1) To a solution of tert-butyl ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(methylthio)methyl]pyridin-3-yl}methyl)carbamate (200 mg, 0.46 mmol) in methanol-water (10:1, 5 mL) was added Oxone (trademark, 310 mg) and then sulfuric acid (50 L) was added. The mixture was stirred at room temperature for 6 hrs. Aqueous saturated sodium hydrogen carbonate 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. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give tert-butyl ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(methylsulfonyl)methyl]pyridin-3-

yl}methyl)carbamate (128 mg, yield 60%) as a white powder.
^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.19-2.28 (1H, m), 2.41 (3H, s), 2.61 (3H, s), 2.74 (3H, s), 2.75 (2H, d, J = 7.2 Hz), 4.25 (2H, d, J = 5.1 Hz), 4.24 (1H, brs), 4.26 (2H, s), 7.71 (2H, d, J =7.8 Hz), 7.26 (2H, d, J = 8.1 Hz).

2) ({2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-[(methylsulfonyl)methyl]pyridin-3-yl}methyl)amine dihydrochloride (36 mg, yield 96%) was obtained as a white powder from tert-butyl ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(methylsulfonyl)methyl]pyridin-3-yl}methyl)carbamate according to a method similar to the method of Example 2-3).
^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 2.17-2.24 (1H, m), 2.40 (3H, s), 2.81 (3H, s), 2.87 (3H, s), 2.89 (2H, brs), 3.68 (2H, brs), 4.40 (2H, s), 7.24 (2H, d, J = 8.1 Hz), 7.35 (2H, d, J = 7.8 Hz), 8.20 (3H, brs).

Example 200

({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)acetic acid dihydrochloride

1) To a solution of [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl methanesulfonate (952 mg, 2 mmol) in N,N-dimethylformamide (5 mL) was added potassium carbonate (415 mg, 3 mmol) and then ethyl mercaptoacetate (240 L, 2.2 mmol) was added. The mixture was stirred at 50 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. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in ethanol (5 mL). 1N Aqueous sodium hydroxide solution (5 mL) was added and the mixture was stirred at room temperature for 2 hrs. 1N Hydrochloric acid (5 mL) 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. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give ({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)acetic acid (265 mg, yield 27%) as a white powder.

^{1}H-NMR (DMSO-d_6) :0.91 (6H, d, J = 6.6 Hz), 1.34 (9H, s), 2.13-2.27 (1H, m), 2.37 (3H, s), 2.55 (2H, d, J = 6.0 Hz), 2.58 (3H, s), 3.09 (2H, s), 3.50 (2H, s), 3.74 (2H, d, J = 4.2 Hz), 6.81 (1H, brs), 7.18 (2H, d, J = 8.1 Hz), 7.24 (2H, d, J = 8.1 Hz), 12.49 (1H, brs).

2) ({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)acetic acid dihydrochloride (106 mg, yield 96%) was obtained as a white powder from ({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)acetic acid according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.14-2.25 (1H, m), 2.42 (3H, s), 2.85 (3H, brs), 3.01 (2H, s), 3.20 (2H, s), 3.59 (2H, s), 3.70 (2H, s), 7.26 (2H, d, J = 8.1 Hz), 7.37 (2H, d, J = 8.1 Hz), 8.23 (3H, brs).

Example 201

({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}sulfonyl)acetic acid dihydrochloride

1) To a solution of ({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)acetic acid (260 mg, 0.55 mmol) in methanol-water (10:1, 5 mL) was added Oxone (trademark, (508 mg) and then sulfuric acid (50 L) was added. The mixture was stirred at room temperature for 6 hrs. Aqueous saturated sodium

hydrogen carbonate 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. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give an oil. ({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}sulfonyl)acetic acid dihydrochloride (104 mg, yield 68%) was obtained as a white powder from the obtained oil according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.95 (6H, d, J = 6.6 Hz), 2.21-2.28 (1H, m), 2.39 (3H, s), 2.65 (3H, s), 2.74 (2H, s), 3.61(2H, s), 4.13 (2H, s), 4.55 (2H, s), 7.18 (2H, d, J = 8.1 Hz), 7.29 (2H, d, J = 7.8 Hz), 8.01 (3H, brs).

Example 202

{[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(1H-tetrazol-5-ylmethyl)pyridin-3-yl]methyl}amine dihydrochloride

1) To a solution of tert-butyl {[5-(cyanomethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (300 mg, 0.74 mmol) in toluene (5 mL) were added dibutyltin oxide (37 mg, 0.15 mmol) and trimethylsilyl azide (292 L, 2.2 mmol) and the mixture was stirred at 80 C for 3 days. 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. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give tert-butyl {[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(1H-tetrazol-5-ylmethyl)pyridin-3-yl]methyl}carbamate (229 mg, yield 69%) as a white powder.

^{1}H-NMR ($CDCl_3$) :0.90 (6H, d, J = 6.6 Hz), 1.36 (9H, s), 2.08-2.11 (1H, m), 2.35 (3H; s), 2.42 (3H, s), 2.83 (2H, s), 4.03(2H, s), 4.09 (2H, brs), 4.79 (1H, brs), 7.01 (2H, d, J = 8.1 Hz), 7.18 (2H, d, J = 7.8 Hz).

2) {[2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-(1H-tetrazol-5-ylmethyl)pyridin-3-yl]methyl}amine dihydrochloride (181 mg, yield 87%) was obtained as a white powder from tert-butyl {[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(1H-tetrazol-5-ylmethyl)pyridin-3-yl]methyl}carbamate according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.15-2.23 (1H, m), 2.36 (3H, s), 2.74 (3H, s), 3.14 (2H, s), 3.78 (2H, s), 4.04 (2H, s), 7.06 (2H, d, J = 8.1 Hz), 7.28 (2H, d, J = 8.1 Hz), 8.35 (3H, brs).

Example 203

3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}-1,2,4-oxadiazol-5(4H)-one dihydrochloride

1) To a solution of tert-butyl {[5-(cyanomethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (400 mg, 1.0 mmol) in ethanol (5 mL) were added sodium carbonate (420 mg, 4.0 mmol) and hydroxy ammonium chloride (210 mg, 3.0 mmol) and the mixture was stirre at 80 C for 3 days. 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. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in tetrahydrofuran (5 mL). N,N'-Carbonyldiimidazole (350 mg, 2.5 mmol) was added and the mixture was stirred at 80 C for 4 hrs. The reaction mixture was concentrated and the obtained residue was purified by silica gel column chromatography to give tert-butyl ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)methyl]pyridin-3-yl}methyl)carbamate (120 mg, yield 26%) as a white powder.

^{1}H-NMR ($CDCl_3$) :0.95 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.06-2.22 (1H, m), 2.40 (3H, s), 2.51 (3H, s), 2.73 (2H, d, J = 7.2 Hz), 3.62(2H, s), 4.02 (2H, d, J = 4.5 Hz), 4.45 (1H, brs),

7.02 (2H, d, J = 8.1 Hz), 7.26 (2H, d, J = 7.8 Hz).

2) 3-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}-1,2,4-oxadiazol-5(4H)-one dihydrochloride (181 mg, yield 87%) was obtained as a white powder from tert-butyl ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)methyl]pyridin-3-yl}methyl)carbamate according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.13-2.21 (1H, m), 2.39 (3H, s), 2.75 (3H, s), 3.05 (2H, brs), 3.66 (2H, s), 3.76 (2H, brs), 7.16 (2H, d, J = 7.8 Hz), 7.36 (2H, d, J = 7.8 Hz), 8.26 (3H, brs).

Example 204

diethyl {[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}phosphonate dihydrochloride

1) Triethyl phosphite (772 L, 4.5 mmol) was added to [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl methanesulfonate (692 mg, 1.45 mmol) and the mixture was stirred at 150 C for 3 hrs. The reaction mixture was allowed to cool to room temperature and purified by silica gel column chromatography to give diethyl {[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}phosphonate (314 mg, yield 42%) as a white powder.

^{1}H-NMR ($CDCl_3$) :0.95 (6H, d, J = 6.6 Hz), 1.17 (6H, t, J = 7.2 Hz), 1.38 (9H, s), 2.14-2.24 (1H, m), 2.40 (3H, s), 2.66 (3H, s), 2.73 (2H, d, J = 5.1 Hz), 2.96 (1H, s), 3.04 (1H, s), 3.86 (4H, q, J = 7.2 Hz), 4.00 (2H, d, J = 4.8 Hz), 4.17 (1H, brs), 7.07 (2H, d, J = 8.1 Hz), 7.24 (2H, d, J = 8.1 Hz).

2) Diethyl {[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}phosphonate dihydrochloride (106 mg, yield 96%) was obtained as a white powder from diethyl {[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}phosphonate according to a

method similar t the method f Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.3 Hz), 1.21 (6H, t, J = 7.2 Hz), 2.11-2.18 (1H, m), 2.42 (3H, s), 2.95 (3H, s), 3.09 (2H, s), 3.17 (2H, s), 3.78 (2H, s), 3.82 (4H, q, J = 7.2 Hz), 7.26 (2H, d, J = 7.8 Hz), 7.39 (2H, d, J = 7.8 Hz), 8.43 (3H, brs).

Example 205

pyridin-2-ylmethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate trihydrochloride

1) Pyridin-2-ylmethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.21 g, yield 99%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.00 g, 2.42 mmol), 2-(bromomethyl)pyridine hydrobromide (0.92 g, 3.64 mmol) and potassium carbonate (1.00 g, 7.27 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.14-2.25 (1H, m), 2.35 (3H, s), 2.56 (3H, s), 2.78 (2H, d, J = 7.2 Hz), 4.14 (2H, brs), 4.25 (1H, brs), 5.06 (2H, s), 6.89 (1H, d, J = 7.7 Hz), 7.06 (2H, d, J = 7.9 Hz), 7.13 (2H, d, J = 7.9 Hz), 7.17-7.22 (1H, m), 7.57 (1H, t, J = 7.7 Hz), 8.52 (1H, d, J = 4.7 Hz).

2) Pyridin-2-ylmethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate trihydrochloride (1.23 g, yield 99%) was obtained as a white solid from pyridin-2-ylmethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.21 g, 2.40 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.4Hz), 2.17-2.28 (1H, m), 2.34 (3H, s), 2.61 (3H, s), 2.94 (2H, d, J = 6.9 Hz), 3.81 (2H, d, J = 4.9 Hz), 5.20 (2H, s), 7.19 (4H, s), 7.23 (1H, brs), 7.62-7.66 (1H, m), 8.06 (1H, t, J = 7.9Hz), 8.39 (3H, brs), 8.68 (1H, d, J = 4.9Hz).

Example 206

benzyl [5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate dihydrochloride

1) Benzyl [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate (305 mg, yield 84%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (300 mg, 0.703 mmol) and benzyl bromide (180 mg, 1.05 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8Hz), 1.38 (9H, s), 2.12-2.28 (1H, m), 2.38 (3H, s), 2.49 (3H, s), 2.76 (2H, d, J = 6.6 Hz), 3.39 (2H, s), 4.03 (2H, d, J = 5.1 Hz), 4.20 (1H, brs), 5.05 (2H, s), 6.90 (2H, d, J = 7.9Hz), 7.14 (2H, d, J = 7.9 Hz), 7.19-7.25 (2H, m), 7.31-7.40 (3H, m).

2) Benzyl [5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate dihydrochloride (214.5 mg, yield 95%) was obtained as a white powder from benzyl [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate (240 mg, 0.464 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6Hz), 2.11-2.27 (1H, m), 2.38 (3H, s), 2.78 (3H, s), 3.15 (2H, s), 3.78 (2H, d, J = 5.1 Hz), 5.04 (2H, s), 7.10 (2H, d, J = 8.1Hz), 7.20-7.45 (7H, m), 8.40 (3H, brs).

Example 207

4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzamide dihydrochloride

1) tert-Butyl {[5-({[4-(aminocarbonyl)phenyl]thio}methyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (360 mg, yield 72%) was obtained as a white s lid from 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoic acid (0.50 g, 0.935 mmol) according to a

method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.13-2.25 (1H, m), 2.38 (3H, s), 2.65 (3H, s), 2.76 (2H, d, J = 7.4 Hz), 3.85 (2H, s), 4.04 (2H, d, J = 5.1Hz), 4.20 (1H, brs), 7.05 (2H, d, J = 7.4 Hz), 7.12 (2H, d, J = 8.5 Hz), 7.19 (2H, d, J = 7.9Hz), 7.64 (2H, d, J = 8.5Hz).

2) 4-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzamide dihydrochloride (253 mg, yield 74%) was obtained as a white solid from tert-butyl ({[5-({[4-(aminocarbonyl)phenyl]thio}methyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (360 mg, 0.674 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.5Hz), 2.13-2.22 (1H, m), 2.37 (3H, s), 2.86 (3H, brs), 3.14 (2H, brs), 3.78 (2H, d, J = 4.7Hz), 3.99 (2H, s), 7.22 (2H, d, J = 8.5Hz), 7.26 (2H, d, J = 8.1Hz), 7.33 (2H, d, J = 8.5Hz), 7.37 (1H, brs) 7.98 (1H, brs), 8.39 (3H, brs).

Example 208

methyl 2-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate dihydrochloride

1) Methyl 2-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate (1.19 g, yield 86%) was obtained as a colorless oil from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.00 g, 2.51 mmol) and methyl 2-mercaptobenzoate (422 mg, 2.51 mmol) according to a method similar to the method of Example 183-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6Hz), 1.39 (9H, s), 2.12-2.26 (1H, m), 2.35 (3H, s), 2.66 (3H, s), 2.75 (2H, d, J = 7.4Hz), 3.77 (2H, s), 3.89 (3H, s), 4.03 (2H, d, J = 4.9Hz), 4.19 (1H, brs), 7.05 (1H, d, J = 8.1Hz), 7.09-7.13 (3H, m), 7.17 (2H, d, J = 8.1Hz), 7.32-7.38 (1H, m), 7.93 (1H, dd, J = 7.7, 1.5 Hz).

2) Methyl 2-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate dihydrochloride (165 mg, yield 91%) was obtained as a white solid from methyl 2-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate (190 mg, 0.346 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.13-2.25 (1H, m), 2.34 (3H, s), 2.77 (3H, brs), 2.98 (2H, brs), 3.69-3.76 (2H, m), 3.80 (3H, s), 3.87 (2H, s), 7.22-7.27 (4H, m), 7.31 (2H, d, J = 8.5Hz), 7.47-7.52 (1H, m), 7.87 (1H, dd, J = 7.7, 1.5 Hz), 8.18 (3H, brs).

Example 209

2-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoic acid

1) 2-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoic acid (0.86 g, yield 88%) was obtained as a white solid from methyl 2-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate (1.00 g, 1.82 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.13-2.24 (1H, m), 2.37 (3H, brs), 2.73 (3H, brs), 2.90 (2H, d, J = 7.0 Hz), 3.77 (2H, s), 4.05 (2H, d, J = 4.5 Hz), 4.32 (1H, brs), 7.01-7.10 (3H, m), 7.16-7.21 (3H, m), 7.30-7.36 (1H, m), 7.94-7.97 (1H, m).

2) 2-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoic acid (274 mg, yield 99%) was obtained as a white solid from 2-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoic acid (0.29 g, 0.542 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.4 Hz), 2.15-2.24 (1H, m), 2.34 (3H, s), 2.81 (3H, brs), 3.03 (2H, brs), 3.66-3.85 (4H, m), 7.19-7.35 (6H, m), 7.44-7.50 (1H, m), 7.88 (1H, d, J = 7.5 Hz), 8.23 (3H, brs).

Example 210

2-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzamide dihydrochloride

1) tert-Butyl {[5-({[2-(aminocarbonyl)phenyl]thio}methyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.23 g, yield 48%) was obtained as a white solid from 2-({[5-({[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoic acid (0.48 g, 0.898 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.14-2.26 (1H, m), 2.40 (3H, s), 2.64 (3H, s), 2.75 (2H, d, J = 7.4 Hz), 3.82 (2H, s), 4.00 (2H, d, J = 5.3 Hz), 4.27 (1H, brs), 5.39 (1H, brs), 6.68 (1H, brs), 6.99 (2H, d, J = 7.9 Hz), 7.19-7.34 (5H, m), 7.75-7.78 (1H, m).

2) 2-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzamide dihydrochloride (218 mg, yield 99%) was obtained as a white solid from tert-butyl {[5-({[2-(aminocarbonyl)phenyl]thio}methyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.23 g, 0.431 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.10-2.24 (1H, m), 2.38 (3H, s), 2.83 (3H, s), 3.18 (2H, brs), 3.79 (2H, d, J = 5.1 Hz), 3.86 (2H, s), 7.16 (2H, d, J = 7.7 Hz), 7.23-7.36 (6H, m), 7.42 (1H, brs), 7.48 (1H, dd, J = 7.4, 1.4 Hz), 7.84 (1H, brs), 8.41 (3H, brs).

Example 211

methyl 3-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate dihydrochloride

1) Methyl 3-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate (1.35 g, yield 82%) was obtained as a brown solid from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.20 g, 3.01 mmol) and methyl 3-mercaptobenzoate (507 mg, 3.01 mmol) according to a method similar to the method of Example 183-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.15-2.24 (1H, m), 2.38 (3H, s), 2.64 (3H, s), 2.75 (2H, d, J = 7.4 Hz), 3.83 (2H, s), 3.90 (3H, s), 4.02 (2H, d, J = 5.1 Hz), 4.22 (1H, brs), 7.00 (2H, d, J = 8.1 Hz), 7.18 (2H, d, J = 7.7 Hz), 7.28-7.30 (1H, m), 7.76-7.79 (1H, m), 7.80-7.84 (1H, m).

2) Methyl 3-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate dihydrochloride (268 mg, yield 87%) was obtained as a white solid from methyl 3-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate (324 mg, 0.590 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 2.11-2.23 (1H, m), 2.36 (3H, s), 2.75 (3H, s), 2.97 (2H, brs), 3.74 (2H, d, J = 4.5 Hz), 3.85 (3H, s), 3.96 (2H, s), 7.19 (2H, d, J = 7.4 Hz), 7.29 (2H, d, J = 7.9 Hz), 7.43 (2H, d, J = 5.1 Hz), 7.65 (1H, s), 7.79-7.83 (1H, m), 8.18 (3H, brs).

Example 212

3-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoic acid dihydrochloride

1) 3-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoic acid (0.73 g, yield 73%) was obtained as a white solid from methyl 3-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoate (0.90 g, 1.64 mmol) according to a method similar t the method

of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.13-2.26 (1H, m), 2.38 (3H, s), 2.68 (3H, s), 2.79 (2H, d, J = 7.0 Hz), 3.85 (2H, s), 4.04 (2H, d, J = 4.9 Hz), 4.24 (1H, brs), 7.00 (2H, d, J = 7.2 Hz), 7.19 (2H, d, J = 7.9 Hz), 7.30-7.35 (2H, m), 7.84 (1H, brs), 7.89 (1H, brs).

2) 3-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoic acid dihydrochloride (167 mg, yield 80%) was obtained as a white solid from 3-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoic acid (0.22 g, 0.441 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.11-2.22 (1H, m), 2.37 (3H, s), 2.84 (3H, brs), 3.10 (2H, brs), 3.76 (2H, d, J = 5.1 Hz), 3.97 (2H, s), 7.21 (2H, d, J = 7.9 Hz), 7.30 (2H, d, J = 7.9 Hz), 7.41-7.42 (2H, m), 7.65 (1H, s), 8.38 (3H, brs).

Example 213

3-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzamide dihydrochloride

1) tert-Butyl {[5-({[3-(aminocarbonyl)phenyl]thio}methyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (460 mg, yield 92%) was obtained as a white solid from 3-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzoic acid (0.50 g, 0.935 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.16-2.27 (1H, m), 2.38 (3H, s), 2.65 (3H, s), 2.75 (2H, d, J = 7.2 Hz), 3.84 (2H, s), 4.02 (2H, d, J = 5.1 Hz), 4.24 (1H, brs), 6.99 (2H, d, J = 7.9 Hz), 7.19 (2H, d, J = 7.7 Hz), 7.25-7.31 (2H, m), 7.49-7.53 (1H; m), 7.56-7.59 (1H, m).

2) 3-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)benzamide dihydrochloride

(439 mg, quant.) was obtained as a white solid from tert-butyl {[5-({[3-(aminocarbonyl)phenyl]thio}methyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (460 mg, 0.862 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.13-2.22 (1H, m), 2.38 (3H, s), 2.86 (3H, s), 3.19 (2H, d, J = 6.6 Hz), 3.78 (2H, d, J = 4.9 Hz), 3.98 (2H, s), 7.23 (2H, d, J = 8.1 Hz), 7.31-7.39 (4H, m), 7.45 (1H, brs), 7.70 (1H, brs), 7.75 (1H, d, J = 7.4 Hz), 8.04 (1H, brs), 8.46 (3H, brs).

Example 214

4-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoic acid dihydrochloride

1) To a solution of tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.50 g, 1.05 mmol), methyl 4-hydroxybenzoate (0.16 g, 1.05 mmol) and triphenylphosphine (0.36 g, 1.37 mmol) in tetrahydrofuran (10 mL) was added 40% solution (0.60 mL, 1.37 mmol) of diethyl azodicarboxylate in toluene and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give methyl 4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoate (380 mg, yield 68%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.16-2.27 (1H, m), 2.34 (3H, s), 2.62 (3H, s), 2.80 (2H, d, J = 7.4 Hz), 3.87 (3H, s), 4.08-4.13 (2H, m), 4.30 (1H, brs), 4.68 (2H, s), 6.80 (2H, d, J = 8.9 Hz), 7.04 (2H, d, J = 7.9 Hz), 7.16 (2H, d, J = 7.7 Hz), 7.93 (2H, d, J = 8.9 Hz).

2) 4-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoic acid (300 mg, yield 81%) was obtained as a white solid from methyl 4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-

methylphenyl)pyridin-3-yl]methoxy}benzoate (380 mg, 0.713 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :1.00 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.17-2.29 (1H, m), 2.35 (3H, s), 2.66 (3H, brs), 2.84 (2H, brs), 4.08-4.14 (2H, m), 4.22-4.25 (1H, m), 4.70 (2H, s), 6.82 (2H, d, J = 8.9 Hz), 7.04 (2H, d, J = 7.9 Hz), 7.17 (2H, d, J = 7.9 Hz), 7.99 (2H, d, J = 8.9 Hz).

3) 4-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoic acid dihydrochloride (267 mg, yield 94%) was obtained as a white solid from 4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoic acid (0.30 g, 0.578 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR ($CDCl_3$) :1.00 (6H, d, J = 6.6 Hz), 2.17-2.26 (1H, m), 2.34 (3H, s), 2.82 (3H, brs), 3.11 (2H, brs), 3.83 (2H, d, J = 5.3 Hz), 4.79 (2H, s), 6.93 (2H, d, J = 8.9 Hz), 7.26 (2H, d, J = 8.1 Hz), 7.31 (2H, d, J = 8.1 Hz), 7.85 (2H, d, J = 8.9 Hz), 8.35 (3H, brs).

Example 215

methyl 4-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoate dihydrochloride

Methyl 4-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoate dihydrochloride (281 mg, yield 99%) was obtained as a white solid from methyl 4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoate (0.30 mg, 0.563 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.18-2.27 (1H, m), 2.33 (3H, s), 2.82 (3H, brs), 3.11 (2H, brs), 3.81-3.83 (5H, m), 4.80 (2H, s), 6.96 (2H, d, J = 8.9 Hz), 7.26 (2H, d, J = 7.9 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.87 (2H, d, J = 8.9 Hz), 8.38 (3H, brs).

Example 216

{[2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amine dihydrochloride

1) To a solution of p-tolualdehyde (8.5 g, 78.3 mmol) and acetone (10 mL) in water (200 mL) was added sodium hydroxide (3.13 g, 78.3 mmol) and the mixture was stirred at room temperature for 3 days. The reaction mixture was diluted with ethyl acetate, washed successively with water and saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 4-(4-methylphenyl)but-3-en-2-one (9.2 g, yield 80%) as an oil. The obtained oil (1.0 g, 6.24 mmol) was dissolved in ethanol (20 mL) and 3-amino-5-methylhex-2-enenitrile (0.93 g, 7.49 mmol) and sodium hydroxide (0.3 g, 7.49 mmol) were added. The mixture was heated under reflux for 2 hrs. The reaction mixture was diluted with ethyl acetate, washed successively with saturated aqueous ammonium chloride solution and saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give a residue. 2-Isobutyl-6-methyl-4-(4-methylphenyl)nicotinonitrile (0.45 g, yield 27%) was obtained as a yellow oil from the obtained residue according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) :1.01 (6H, d, J = 6.6 Hz), 2.20-2.33 (1H, m), 2.43 (3H, s), 2.63 (3H, s), 2.96 (2H, d, J = 7.4 Hz), 7.11 (1H, s), 7.31 (2H, d, J = 7.9 Hz), 7.47 (2H, d, J = 8.3 Hz).

2) {[2-Isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amine dihydrochloride (456 mg, yield 78%) was obtained as a white solid from 2-isobutyl-6-methyl-4-(4-methylphenyl)nicotinonitrile (0.45 g, 1.70 mmol) according to a method similar to the method of Example 108-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.4 Hz), 2.13-2.22 (1H, m), 2.41 (3H, s), 2.72-2.82 (3H, m), 3.05-3.18 (2H, m), 4.02-4.11 (2H, m), 7.41 (4H, s), 7.67 (1H, brs), 8.47-8.58 (3H, m).

Example 217

((2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]pyridin-3-yl)methyl)amine 4-methylbenzenesulfonate

1) To a solution of sodium 4-methylbenzenesulfinate (9.00 g, 50.5 mmol) in ethanol (50 mL) was added bromoacetone (6.9 g, 50 mmol) and the mixture was heated under reflux for 30 min. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give 1-[(4-methylphenyl)sulfonyl]acetone (8.0 g, yield 75%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) : 2.41 (3H, s), 2.46 (3H, s), 4.14 (2H, s), 7.37 (2H, d, J = 8.2 Hz), 7.77 (2H, d, J = 8.2 Hz).

2) A mixture of 1-[(4-methylphenyl)sulfonyl]acetone (2.0 g, 9.4 mmol), p-tolualdehyde (1.1 g, 9.4 mmol), piperidine (0.093 mL, 0.94 mmol), acetic acid (0.11 mL, 1.9 mmol) and toluene (100 mL) was heated under reflux using a Dean-Stark trap for 3 hrs. The reaction mixture was allowed to cool to room temperature, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 4-(4-methylphenyl)-3-[(4-methylphenyl)sulfonyl]but-3-en-2-one as a crude product (3.5 g). A mixture of the crude product (1.73 g), 3-amino-5-methylhex-2-enenitrile (0.65 g, 5.23 mmol) and ethanol (50 mL) was heated under reflux for 12 hrs. The reaction mixture was allowed to cool to room temperature, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography and the obtained solid was recrystallized from diisopropyl ether-ethyl acetate to give 2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]-1,4-dihydropyridine-3-carbonitrile (1.3 g, yield 64%) as a white powder.

melting point: 135-137 C

3) 2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]nicotinonitrile (0.77 g, yield 68%) was obtained as a white powder from 2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]-1,4-dihydropyridine-3-carbonitrile (1.1 g, 2.7 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) : 0.99 (6H, d, J = 6.6 Hz), 2.20-2.35 (1H, m), 2.38 (3H, s), 2.39 (3H, s), 2.91 (2H, d, J = 7.2 Hz), 3.07 (3H, s), 6.86 (2H, d, J = 8.1 Hz), 7.08 (4H, d, J = 8.1 Hz), 7.23 (2H, d, J = 8.1 Hz).

4) ({2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]pyridin-3-yl}methyl)amine (0.64 g, yield 93%) was obtained as a colorless oil from 2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]nicotinonitrile (0.69 g, 1.6 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) : 0.96 (6H, d, J = 6.6 Hz), 1.41 (2H, brs), 2.20-2.35 (1H, m), 2.38 (6H, s), 2.79 (2H, d, J = 7.2 Hz), 2.96 (3H, s), 3.40 (2H, s), 6.76 (2H, d, J = 8.1 Hz), 7.03 (2H, d, J = 8.3 Hz), 7.09 (2H, d, J = 8.1 Hz), 7.27 (2H, d, J = 8.3 Hz).

5) ({2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]pyridin-3-yl}methyl)amine (0.64 g, 1.5 mmol) was dissolved in ethanol (5 mL) and a solution of p-toluenesulfonic acid hydrate (0.29 g, 1.5 mmol) in ethanol (5 mL) was added dropwise with stirring at room temperature. The mixture was stirred at room temperature for 10 min. The precipitate was collected by filtration, washed with cooled ethanol and dried to give ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-methylphenyl)sulfonyl]pyridin-3-yl}methyl)amine 4-methylbenzenesulfonate (0.57 g, yield 63%) as a white powder.

^{1}H-NMR (DMSO-d_6) : 0.94 (6H, d, J = 6.6 Hz), 2.15-2.30 (1H, m), 2.29 (3H, s), 2.37 (6H, s), 2.78 (2H, d, J = 7.0 Hz), 2.84 (3H,

s), 3.57 (2H, s), 6.87 (2H, d, J = 7.9 Hz), 7.11 (4H, d, J = 8.5 Hz), 7.25-7.30 (4H, m), 7.47 (2H, d, J = 7.9 Hz), 7.76 (3H, brs).

Example 218

{[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(methylsulfonyl)pyridin-3-yl]methyl}amine

1) A mixture of 1-(methylsulfonyl)acetone (3.68 g, 27 mmol), p-tolualdehyde (3.24 g, 27 mmol), piperidine (0.26 mL, 2.7 mmol), acetic acid (0.31 mL, 5.4 mmol) and toluene (200 mL) was heated under reflux using a Dean-Stark trap for 12 hrs. The reaction mixture was allowed to cool to room temperature, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in methanol (20 mL). 3-Amino-5-methylhex-2-enenitrile (4.3 g, 35 mmol) was added and the mixture was heated under reflux for 6 hrs. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give 2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(methylsulfonyl)-1,4-dihydropyridine-3-carbonitrile (6.38 g, yield 68%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) :0.95 (3H, d, J = 6.6 Hz), 1.01 (3H, d, J = 6.6 Hz), 2.18-2.25 (1H, m), 2.32 (3H, s), 2.35 (3H, s), 2.40 (3H, s), 2.44 (1H, s), 3.04 (1H, s), 4.69 (1H, s), 5.80 (1H, s), 7.14 (2H, d, J = 8.1 Hz), 7.21 (2H, d, J = 8.3 Hz).

2) 2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-(methylsulfonyl)nicotinonitrile (4.14 g, yield 65%) was obtained as a white solid from 2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(methylsulfonyl)-1,4-dihydropyridine-3-carbonitrile (6.38 g, 18.6 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) :1.02 (6H, d, J = 6.8 Hz), 2.23-2.37 (1H, m), 2.44 (3H, s), 2.95 (2H, d, J = 7.2 Hz), 3.05 (3H, s), 7.24 (2H, d, J = 8.1 Hz), 7.33 (2H, d, J = 7.9 Hz).

3) {[2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-(methylsulfonyl)pyridin-3-yl]methyl}amine (0.81 g, yield 75%) was obtained as a white solid from 2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(methylsulfonyl)nicotinonitrile (1.06 g, 3.09 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.8 Hz), 2.22-2.36 (1H, m), 2.43 (3H, s), 2.80 (3H, s), 2.82 (2H, d, J = 7.4 Hz), 2.96 (3H, s), 3.50 (2H, s), 7.12 (2H, d, J = 7.9 Hz), 7.26 (2H, d, J = 7.7 Hz).

Example 219

methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoate dihydrochloride

1) Methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoate (730 mg, yield 72%) was obtained as a colorless oil from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.75 g, 1.89 mmol) and methyl 3-hydroxybenzoate (0.29 g, 1.90 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.19-2.28 (1H, m), 2.35 (3H, s), 2.62 (3H, s), 2.79 (2H, d, J = 7.2 Hz), 3.89 (3H, s), 4.07-4.11 (2H, m), 4.67 (2H, s), 6.98-7.02 (1H, m), 7.05 (2H, d, J = 7.9 Hz), 7.16 (2H, d, J = 7.7 Hz), 7.29-7.32 (1H, m), 7.42-7.43 (1H, m), 7.60-7.63 (1H, m).

2) Methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoate dihydrochloride (116 mg, yield 85%) was obtained as a white solid from methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoate (144 mg, 0.270 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.17-2.26 (1H, m), 2.34 (3H, s), 2.83 (3H, brs), 3.11 (2H, brs), 3.83 (5H, s), 4.79 (2H, s), 7.15 (1H, dd, J = 7.8, 2.2 Hz), 7.27 (2H, d, J =

8.3 Hz), 7.29-7.35 (3H, m), 7.42 (2H, t, J = 7.9 Hz), 7.56 (1H, d, J = 7.7 Hz), 8.38 (3H, brs).

Example 220

3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoic acid dihydrochloride

1) 3-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoic acid (460 mg, yield 80%) was obtained as a colorless oil from methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoate (0.58 g, 1.10 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.17-2.28 (1H, m), 2.34 (3H, s), 2.65 (3H, s), 2.82 (2H, d, J = 7.2 Hz), 4.11 (2H, brs), 4.28 (1H, brs), 4.68 (2H, s), 7.03-7.07 (3H, m), 7.16 (2H, d, J = 7.9 Hz), 7.33 (1H, t, J = 8.0 Hz), 7.47 (1H, brs), 7.64-7.70 (1H, m).

2) 3-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoic acid dihydrochloride (128 mg, yield 99%) was obtained as a white solid from 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoic acid (136 mg, 0.262 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.2 Hz), 2.18-2.27 (1H, m), 2.34 (3H, s), 2.73-2.79 (3H, m), 3.04 (2H, brs), 3.81 (2H, brs), 4.76 (2H, s), 7.11 (2H, d, J = 8.1 Hz), 7.21-7.31 (5H, m), 7.38 (1H, t, J = 7.7 Hz), 7.54 (1H, d, J = 7.5 Hz), 8.27 (3H, brs).

Example 221

methyl 2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoate dihydrochloride

1) Methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-

yl]methoxy}benzoate (700 mg, yield 70%) was obtained as a white solid from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.75 g, 1.89 mmol) and methyl 2-hydroxybenzoate (0.29 g, 1.90 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.19-2.28 (1H, m), 2.36 (3H, s), 2.67 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 3.81 (3H, s), 4.09 (2H, d, J = 4.0 Hz), 4.23 (1H, brs), 4.71 (2H, s), 6.66 (1H, d, J = 8.3 Hz), 6.93-6.98 (1H, m), 7.04 (2H, d, J = 8.1 Hz), 7.16 (2H, d, J = 7.7 Hz), 7.29-7.35 (1H, m), 7.72 (1H, dd, J = 7.6, 1.8 Hz).

2) Methyl 2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoate dihydrochloride (42.3 mg, yield 56%) was obtained as a white solid from methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoate (78.8 mg, 0.148 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.18-2.29 (1H, m), 2.36 (3H, s), 2.83 (3H, brs), 3.07 (2H, brs), 3.74 (3H, s), 3.83 (2H, d, J = 4.7 Hz), 4.78 (2H, s), 6.91 (1H, d, J = 8.5 Hz), 7.03 (2H, t, J = 7.4 Hz), 7.25 (2H, d, J = 7.9 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.42-7.48 (1H, m), 7.64 (1H, dd, J = 7.6, 1.6 Hz), 8.30 (3H, brs).

Example 222

2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoic acid dihydrochloride

1) 2-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoic acid (140 mg, yield 23%) was obtained as a white solid from methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoate (0.62 g, 1.17 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.21-

2.30 (1H, m), 2.34 (3H, s), 2.65 (3H, s), 2.81 (2H, d, J = 7.4 Hz), 4.10 (2H, d, J = 5.3 Hz), 4.92 (2H, s), 6.83 (1H, d, J = 8.3 Hz), 7.01 (2H, d, J = 8.1 Hz), 7.10-7.15 (1H, m), 7.17 (2H, d, J = 7.7 Hz), 7.44-7.50 (1H, m), 8.17 (1H, dd, J = 7.8, 1.8 Hz).

2) 2-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoic acid dihydrochloride (103 mg, yield 77%) was obtained as a white solid from 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoic acid (0.14 g, 0.270 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.18-2.27 (1H, m), 2.37 (3H, s), 2.89 (3H, brs), 3.13 (2H, brs), 3.84 (2H, d, J = 4.7 Hz), 4.78 (2H, s), 6.86 (1H, d, J = 8.5 Hz), 7.02 (1H, t, J = 7.4 Hz), 7.27 (2H, d, J = 7.9 Hz), 7.32 (2H, d, J = 8.1 Hz), 7.38-7.44 (1H, m), 7.61 (1H, dd, J = 7.5, 1.7 Hz), 8.39 (3H, brs).

Example 223

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]benzamide dihydrochloride

To a solution of tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) in tetrahydrofuran (3 mL) was added benzoyl chloride (88 L, 0.75 mmol) and triethylamine (140 L, 1.0 mmol) was added. The mixture was stirred for 30 min. Saturated aqueous sodium hydroxide solution (5 mL) 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. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give an oil. To a solution of the obtained oil in ethyl acetate (1 mL) was added 4N hydrogen chloride ethyl acetate solution (1 mL) and the mixture

was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from hexane to give N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]benzamide dihydrochloride (203 mg, yield 96%) as a white powder.

^{1}H-NMR (DOSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.20-2.32 (1H, m), 2.31 (3H, s), 2.64 (3H, s), 3.11 (2H, s), 3.87 (2H, s), 7.17-7.66 (9H, m), 8.49 (3H, brs), 10.13 (1H, brs).

Example 224

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-2-phenylacetamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-2-phenylacetamide dihydrochloride (208 mg, yield 95%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and phenylacetyl chloride (100 L, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 1.98-2.26 (1H, m), 2.40 (3H, s), 2.50 (3H, s), 3.04 (2H, s), 3.40 (2H, s), 3.78 (2H, s), 6.94-6.97 (2H, m), 7.12-7.53 (7H, m), 8.44 (3H, brs), 9.90 (1H, brs).

Example 225

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-phenylpropanamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-phenylpropanamide dihydrochloride (208 mg, yield 92%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and hydrocinnamoyl chloride (111 L, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 2.15-2.23 (1H, m), 2.33 (2H, t, J = 7.2 Hz), 2.37 (6H, s), 2.63 (2H, t, J = 7.2

Hz), 2.94 (2H, brs), 3.79 (2H, s), 7.10-7.29 (9H, m), 8.26 (3H, brs), 9.43 (1H, brs).

Example 226

(2E)-N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-phenylacrylamide dihydrochloride

(2E)-N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-phenylacrylamide dihydrochloride (208 mg, yield 92%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and cinnamoyl chloride (125 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.15-2.28 (1H, m), 2.34 (3H, s), 2.55 (3H, s), 3.02 (2H, brs), 3.83 (2H, brs), 6.63 (1H, d, J = 15.6 Hz), 7.16-7.23 (2H, m), 7.28-7.32 (2H, m), 7.39-7.46 (4H, m), 7.52-7.56 (2H, m), 8.36 (3H, brs), 9.76 (1H, brs).

Example 227

ethyl [({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl) pyridin-3-yl]amino}carbonyl)oxy]acetate dihydrochloride

1) Ethyl [({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)oxy]acetate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and ethyl hydroxyacetate (104 mg, 2.0 mmol) according to a method similar to the method of Example 95-1).

EIMS(M+1):514

2) Ethyl [({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)oxy]acetate dihydrochloride (202 mg, yield 45%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.3 Hz), 1.18 (3H, t, J = 7.2 Hz), 2.11-2.29 (1H, m), 2.38 (3H, s), 2.86 (3H, s), 3.77 (2H, brs), 3.91 (2H, brs), 4.12 (2H, q, J = 7.2 Hz), 4.52 (2H, s), 7.15 (2H, d, J = 7.8 Hz), 7.29 (2H, d, J = 7.8 Hz), 8.21 (3H, brs), 9.12 (1H, brs).

Example 228

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N'-benzylurea dihydrochloride

1) tert-Butyl {[5-{[(benzylamino)carbonyl]amino}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and benzylamine (218 L, 2.0 mmol) according to a method similar to the method of Example 95-1).

EIMS(M+1):517

2) N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N'-benzylurea dihydrochloride (181 mg, yield 40%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.3 Hz), 2.09-2.22 (1H, m), 2.41 (3H, s), 2.50 (3H, s), 2.65 (2H, brs), 3.81 (2H, brs), 4.19(2H, brs), 7.11-7.35 (9H, m), 8.43 (3H, brs).

Example 229

methyl 4-{[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)oxy]methyl}benzoate dihydrochloride

1) Methyl 4-{[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)oxy]methyl}benzoate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and methyl 4-hydroxymethylbenzoate (250 mg, 1.5 mmol) according t a method similar to the method of Example 95-1).

EIMS (M+1) : 576

2) Methyl 4-{[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)oxy]methyl}benzoate dihydrochloride (195 mg, yield 38%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.3 Hz), 2.14-2.23 (1H, m), 2.39 (3H, s), 2.55 (3H, s), 2.97 (2H, brs), 3.78 (2H, brs), 3.87 (3H, s), 5.09 (2H, brs), 7.14-7.29 (6H, m), 7.92 (2H, d, J = 8.4 Hz), 8.30 (3H, brs), 9.19 (1H, brs).

Example 230

3-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]benzoic acid dihydrochloride

1) To a solution of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.70 g, 4.12 mmol) in N,N-dimethylformamide (15 mL) were added methyl 3-(bromomethyl)benzoate (0.79 g, 3.43 mmol) and potassium carbonate (0.71 g, 5.15 mmol) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate, and the mixture was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give 3-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.80 g, yield 94%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.16-2.25 (1H, m), 2.33 (3H, s), 2.53 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.94 (3H, s), 4.13 (2H, brs), 4.20 (1H, brs), 4.95 (2H, s), 7.01 (2H, d, J = 8.1 Hz), 7.09 (2H, d, J = 7.9 Hz), 7.22 (1H, d, J = 7.7 Hz), 7.35 (1H, t, J = 7.7 Hz), 7.83 (1H, s), 7.98 (1H, d, J = 7.7 Hz).

2) 3-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-

methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]benzoic acid (1.43 g, yield 87%) was obtained as a colorless oil from 3-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.69 g, 3.01 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.13-2.25 (1H, m), 2.34 (3H, s), 2.55 (3H, s), 2.80 (2H, d, J = 7.4 Hz), 4.11-4.16 (2H, m), 4.22 (1H, brs), 4.98 (2H, s), 7.02 (2H, d, J = 7.9 Hz), 7.11 (2H, d, J = 7.7 Hz), 7.26-7.30 (1H, m), 7.39 (1H, t. J = 7.7 Hz), 7.89 (1H, s), 8.04 (1H, d, J = 7.5 Hz).

3) 3-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]benzoic acid dihydrochloride (293 mg, yield 60%) was obtained as a white solid from 3-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]benzoic acid (0.50 g, 0.927 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.16-2.25 (1H, m), 2.32 (3H, s), 2.54 (3H, s), 2.90 (2H, d, J = 6.6 Hz), 3.81 (2H, d, J = 5.1 Hz), 5.04 (2H, s), 7.13 (2H, d, J = 8.5 Hz), 7.17 (2H, d, J = 8.3 Hz), 7.26-7.30 (1H, m), 7.44 (1H, t. J = 7.6 Hz), 7.73-7.74 (1H, m), 7.89-7.92 (1H, m), 8.30 (3H, brs).

Example 231

2-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]benzoic acid dihydrochloride

1) To a solution of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.10 g, 2.67 mmol) in N,N-dimethylformamide (15 mL) were added 2-bromobenzyl bromide (0:61 g, 2.43 mmol) and potassium carbonate (0.51 g, 3.65 mmol) and the mixture was stirred at room temperature f r 1 hr. The reaction mixture was diluted with

ethyl acetate, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give 2-bromobenzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.23 g, yield 87%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8 Hz), 1.38 (9H, s), 2.14-2.25 (1H, m), 2.35 (3H, s), 2.56 (3H, s), 2.78 (2H, d, J = 7.2 Hz), 4.11-4.13 (2H, m), 4.22 (1H, brs), 5.05 (2H, s), 7.02-7.05 (3H, m), 7.11 (2H, d, J = 7.9 Hz), 7.16-7.21 (2H, m), 7.51-7.54 (1H, m).

2) 2-Bromobenzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.23 g, 2.12 mmol), triethylamine (0.59 mL, 4.24 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (174 mg, 0.212 mmol) were dissolved in methanol (5 mL) - N,N-dimethylformamide (15 mL) and the resulting mixture was stirred under a carbon monoxide atmosphere for 14 hrs. The reaction mixture was diluted with ethyl acetate (100 mL) and the mixture was washed with saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give 2-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.88 g, yield 74%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.16-2.25 (1H, m), 2.35 (3H, s), 2.56 (3H, s), 2.78 (2H, d, J = 7.2 Hz), 3.87 (3H, s), 4.11-4.16 (2H, m), 4.21 (1H, brs), 5.39 (2H, s), 7.01-7.06 (3H, m), 7.11 (2H, d, J = 7.9 Hz), 7.32-7.42 (2H, m), 7.93-7.96 (1H, m).

3) 2-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]benzoic acid (0.75 g, yield 89%) was

obtained as a colorless oil from 2-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.88 g, 1.54 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.37 (9H, s), 2.12-2.21 (1H, m), 2.36 (3H, s), 2.54 (3H, s), 2.83 (2H, d, J = 7.2 Hz), 4.13-4.18 (2H, m), 4.25 (1H, brs), 5.38 (2H, s), 7.01-7.04 (3H, m), 7.11 (2H, d, J = 7.5 Hz), 7.38-7.46 (2H, m), 8.06-8.09 (1H, m).

4) 2-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]benzoic acid dihydrochloride (278 mg, yield 65%) was obtained as a white solid from 2-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]benzoic acid (0.45 g, 0.823 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.18-2.27 (1H, m), 2.35 (3H, s), 2.84 (2H, d, J = 7.2 Hz), 3.82 (2H, d, J = 5.3 Hz), 5.32 (2H, s), 6.97-7.00 (1H, m), 7.18 (2H, d, J = 8.3 Hz), 7.24 (2H, d, J = 7.9 Hz), 7.41-7.51 (2H, m), 7.87-7.91 (1H, m), 8.19 (3H, brs).

Example 232

methyl 4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoate dihydrochloride

Methyl 4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoate dihydrochloride (230 mg, yield 89%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and terephthalic acid monomethyl ester chloride (149 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.22-2.31 (1H, m),

2.31 (3H, s), 2.54 (3H, s), 2.95 (2H, brs), 3.85 (2H, brs), 3.87 (3H, s), 7.20-7.27 (4H, m), 7.72 (2H, d, J = 8.4 Hz), 7.99 (2H, d, J = 8.4 Hz), 8.26 (3H, brs), 10.13 (1H, brs).

Example 233

4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoic acid dihydrochloride

1) 4-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoic acid (248 mg, yield 98%) was obtained as a white powder from methyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoate (260 mg, 0.48 mmol) according to a method similar to the method of Example 36-1).

^{1}H-NMR (DMSO-d_6). :0.98 (6H, d, J = 6.6 Hz), 1.35 (9H, s), 2.18-2.29 (1H, m), 2.29 (3H, s), 2.59 (3H, s), 2.88 (2H, brs), 3.99 (2H, brs), 7.14 (1H, s), 7.20 (4H, s), 7.70 (2H, d, J = 8.4 Hz), 7.97 (2H, d, J = 8.4 Hz), 10.13 (1H, brs).

2) 4-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoic acid dihydrochloride (230 mg, yield 99%) was obtained as a white powder from 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoic acid (248 mg, 0.47 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.22-2.32 (1H, m), 2.31 (3H, s), 2.55 (3H, s), 2.96 (2H, brs), 3.83 (2H, brs), 7.20-7.27 (4H, m), 7.70 (2H, d, J = 8.1 Hz), 7.96 (2H, d, J = 8.1 Hz), 8.26 (3H, brs), 10.11 (1H, brs).

Example 234

methyl (4-{[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}phenyl)acetate dihydrochloride

1) Methyl (4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-

yl]methoxy}phenyl)acetate (0.36 g, yield 61%) was obtained as a white powder from tert-butyl {[5-(hydroxymethyl)-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (0.44 g, 1.1 mmol) and methyl 4-hydroxyphenylacetate (0.18 g, 1.1 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) : 1.03 (9H, s), 1.37 (9H, s), 2.36 (3H, s), 2.61 (3H, s), 2.87 (2H, s), 3.55 (2H, s), 3.68 (3H, s), 4.05-4.25 (3H, m), 4.59 (2H, s), 6.76 (2H, d, J = 8.5 Hz), 7.05 (2H, d, J = 8.5 Hz), 7.14 (2H, d, J = 8.5 Hz), 7.17 (2H, d, J = 8.5 Hz).

2) Methyl (4-{[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}phenyl)acetate dihydrochloride (0.088 g, yield 74%) was obtained as a white powder from methyl (4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}phenyl)acetate (0.13 g, 0.22 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) : 1.04 (9H, s), 2.35 (3H, s), 2.77 (3H, brs), 3.14 (2H, brs), 3.58 (2H, d, J = 7.0 Hz), 3.59 (3H, s), 3.87 (2H, s), 4.66 (2H, s), 6.80 (2H, d, J = 8.7 Hz), 7.14 (2H, d, J = 8.7 Hz), 7.25 (2H, d, J = 7.7 Hz), 7.31 (2H, d, J = 7.7 Hz), 8.20 (3H, brs).

Example 235

methyl 2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-1,3-oxazole-4-carboxylate dihydrochloride

1) Methyl N-{[5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}serinate (5.37 g, yield 87%) was obtained as a colorless oil from 5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (5.00 g, 11.2 mmol) and serine methyl ester hydrochloride (2.09 g, 13.4 mmol) according to a method similar to the method of Example 195-2).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 5.7 Hz), 2.15-2.26 (1H, m), 2.38 (3H, s), 2.57 (3H, s), 2.80 (2H, d, J = 7.0 Hz), 3.36-3.42 (1H, m), 3.61-3.69 (1H, m), 3.73 (3H, s), 4.19-4.29 (2H, m),

4.43-4.52 (2H, m), 5.03 (2H, s), 6.21 (1H, d, J = 7.0 Hz), 7.12-7.17 (2H, m), 7.17-7.22 (2H, m), 7.29-7.38 (5H, m).

2) A solution of methyl N-{[5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}serinate (5.37 g, 9.81 mmol) in dichloromethane (50 mL) was cooled to -78 C and diethylaminosulfur trifluoride (1.72 mL, 11.8 mmol) was added. The mixture was stirred at the same temperature for 1 hr. Potassium carbonate (1.36 g, 14.7 mmol) was added and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give methyl 2-[5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4,5-dihydro-1,3-oxazole-4-carboxylate (3.59 g, yield 69%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) :0.95 (6H, d, J = 6.6 Hz), 2.15-2.26 (1H, m), 2.37 (3H, s), 2.57 (3H, s), 2.81 (2H, d, J = 7.2 Hz), 3.71 (3H, s), 4.11-4.16 (1H, m), 4.23 (2H, d, J = 5.5 Hz), 4.33 (1H, dd, J = 8.8, 7.4 Hz), 4.59-4.65 (1H, m), 5.03 (2H, s), 7.05 (2H, d, J = 8.5 Hz), 7.13-7.21 (2H, m), 7.29-7.38 (5H, m).

3) A solution of methyl 2-[5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4,5-dihydro-1,3-oxazole-4-carboxylate (0.83 g, 2.12 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (1.11 mL, 7.42 mmol) in dichloromethane (10 mL) was cooled to 0 C and bromotrichloromethane (0.73 mL, 7.42 mmol) was added. The mixture was stirred at the same temperature for 1 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous ammonium chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give methyl 2-[5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-1,3-oxazole-4-carboxylate (520 mg, yield 63%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) :1.03 (6H, d, J = 6.8 Hz), 2.24-2.34 (4H, m), 2.59 (3H, s), 3.00 (2H, d, J = 7.4 Hz), 3.92 (3H, s), 7.11 (2H, d, J = 8.5 Hz), 7.16 (2H, d, J = 8.3 Hz), 8.08 (1H, s).

4) Methyl 2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-1,3-oxazole-4-carboxylate dihydrochloride (456 mg, yield 73%) was obtained as a white solid from methyl 2-[5-cyano-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-1,3-oxazole-4-carboxylate (0.52 g, 1.34 mmol) according to a method similar to the method of Example 108-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.21-2.30 (4H, m), 2.45-2.48 (3H, m), 2.90-3.02 (2H, m), 3.78 (3H, s), 3.85 (2H, d, J = 4.7 Hz), 7.11 (2H, dd, J = 8.1, 2.1 Hz), 7.20 (2H, d, J = 8.1 Hz), 8.30-8.47 (3H, m), 8.77 (1H, d, J = 1.5 Hz).

Example 236

2-(4-{[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}phenyl)acetamide dihydrochloride

1) tert-Butyl {[5-{[4-(2-amino-2-oxoethyl)phenoxy]methyl}-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (0.14 g, yield 47%) was obtained as a white powder from tert-butyl {[5-(hydroxymethyl)-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (0.22 g, 0.53 mmol) and 4-hydroxyphenylacetamide (0.081 g, 0.53 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) : 1.04 (9H, s), 1.37 (9H, s), 2.36 (3H, s), 2.62 (3H, s), 2.88 (2H, s), 3.51 (2H, s), 4.10-4.25 (3H, m), 4.61 (2H, s), 5.35 (2H, brs), 6.75-6.80 (2H, m), 7.05 (2H, d, J = 7.9 Hz), 7.10-7.20 (4H, m).

2) 2-(4-{[5-(Aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}phenyl)acetamide dihydrochloride (0.098 g, yield 92%) was obtained as a pale-yellow powder from tert-butyl {[5-{[4-(2-amino-2-oxoethyl)phenoxy]methyl}-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (0.11 g, 0.20 mmol) according to a method

similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) : 1.05 (9H, s), 2.36 (3H, s), 2.79 (3H, brs), 3.05-3.25 (2H, m), 3.28 (2H, s), 3.88 (2H, brs), 4.66 (2H, s), 6.79 (2H, d, J = 8.5 Hz), 6.83 (1H, brs), 7.14 (2H, d, J = 8.5 Hz), 7.26 (2H, d, J = 7.4 Hz), 7.33 (2H, d, J = 7.4 Hz), 7.42 (1H, brs), 8.19 (3H, brs).

Example 237

methyl (4-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}phenyl)acetate

1) Methyl (4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}phenyl)acetate (570 mg, yield 83%) was obtained as a colorless oil from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (500 mg, 1.25 mmol) and methyl (4-hydroxyphenyl)acetate (250 mg, 1.51 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.17-2.30 (1H, m), 2.36 (3H, s), 2.62 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 3.51 (2H, s), 3.56 (3H, s), 4.10 (2H, d, J = 4.7 Hz), 4.20 (1H, s), 4.61 (2H, s), 6.78 (2H, d, J = 8.5 Hz), 7.06 (2H, d, J = 8.5 Hz), 7.12-7.20 (4H, m).

2) Methyl (4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}phenyl)acetate (570 mg, 1.04 mmol) was dissolved in trifluoroacetic acid (10 mL) and the mixture was stirred for 1 hr. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl (4-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}phenyl)acetate (300 mg, yield

65%) as a colorless oil.

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.18-2.25 (1H, m), 2.34 (3H, s), 2.60 (3H, s), 2.88 (2H, d, J = 7.4 Hz), 3.30 (2H, d, J = 5.3 Hz), 3.61 (3H, s), 4.20 (2H, d, J = 4.7 Hz), 4.60 (2H, s), 6.70 (2H, d, J = 8.5 Hz), 6.79 (2H, d, J = 8.5 Hz), 7.05 (2H, d, J = 8.3 Hz), 7.15 (2H, d, J = 8.3 Hz).

Example 238

3-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoic acid dihydrochloride

3-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoic acid dihydrochloride (230 mg, yield 89%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and isophthalic acid monomethyl ester chloride (149 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :1.01 (6H, d, J = 6.6 Hz), 2.18-2.31 (1H, m), 2.31 (3H, s), 2.60 (3H, s), 3.04 (2H, brs), 3.85 (2H, brs), 7.25 (4H, s), 7.57 (1H, t, J = 7.8 Hz), 7.86 (1H, d, J = 7.8 Hz), 8.07 (1H, d, J = 7.8 Hz), 8.16 (1H, s), 8.36 (3H, brs), 10.19 (1H, brs).

Example 239

methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1H-indole-2-carboxylate

1) Methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1H-indole-2-carboxylate (0.41 g, yield 52%) was obtained as a pale-yellow solid from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.60 g, 1.49 mmol) and methyl 3-hydroxyindole-2-carboxylate (0.26 g, 1.36 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8 Hz), 1.37 (9H, s), 2.17-2.26 (1H, m), 2.37 (3H, s), 2.77 (2H, d, J = 7.2 Hz), 2.86 (3H, s), 3.82 (3H, s), 4.00 (2H, d, J = 4.5 Hz), 4.09 (1H, brs), 5.03 (2H, s), 6.74-6.89 (4H, m), 7.09 (2H, d, J = 7.9 Hz), 7.21-7.31 (2H, m), 8.28 (1H, brs).

2) Methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1H-indole-2-carboxylate (0.26 g, 1.36 mmol) was dissolved in 4N hydrogen chloride ethyl acetate solution (10 mL) and the mixture was stirred at room temperature for 30 min. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained yellow solid was recrystallized from ethyl acetate-hexane to give methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1H-indole-2-carboxylate (256 mg, yield 75%) as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 2.17-2.30 (1H, m), 2.38 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 2.86 (3H, s), 3.51 (2H, s), 3.83 (3H, s), 5.02 (2H, s), 6.77-6.88 (4H, m), 7.10 (2H, d, J = 7.7 Hz), 7.22-7.28 (2H, m), 8.27 (1H, brs).

Example 240

4-cyanobenzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate

1) 4-Cyanobenzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (2.32 g, yield 86%) was obtained as a yellow oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (2.10 g, 5.10 mmol) and 4-cyanobenzyl bromide (1.00 g, 5.10 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8 Hz), 1.38 (9H, s), 2.17-2.26 (1H, m), 2.37 (3H, s), 2.54 (3H, s), 2.78 (2H, d, J = 7.2

Hz), 4.11-4.13 (2H, m), 4.20 (1H, brs), 4.98 (2H, s), 7.01 (2H, d, J = 8.1 Hz), 7.10 (4H, d, J = 8.1 Hz), 7.54 (2H, d, J = 8.3 Hz).

2) 4-Cyanobenzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.52 g, 0.985 mmol) was dissolved in trifluoroacetic acid (10 mL) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and extracted twice with ethyl acetate. The extract was dried over anhydrous magnesium sulfate to give 4-cyanobenzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.42 g, yield 99%) as a yellow oil.
^{1}H-NMR ($CDCl_3$) :0.90 (6H, d, J = 6.6 Hz), 2.08-2.17 (1H, m), 2.32 (3H, s), 2.54 (3H, s), 2.70 (2H, d, J = 7.0 Hz), 3.97 (2H, s), 4.99 (2H, s), 7.00 (2H, d, J = 8.1 Hz), 7.08-7.14 (4H, m), 7.54 (2H, d, J = 8.3 Hz).

Example 241

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]quinoxaline-2-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]quinoxaline-2-carboxamide dihydrochloride (137 mg, yield 50%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and quinoxaline-2-carbonyl chloride (144 mg, 0.75 mmol) according to a method similar to the method of Example 223.
^{1}H-NMR (DMSO-d_6) :1.02 (6H, d, J = 6.6 Hz), 2.22-2.29 (1H, m), 2.23 (3H, s), 2.64 (3H, s), 3.06 (2H, brs), 3.86 (2H, brs), 7.22 (2H, d, J = 8.1 Hz), 7.29 (2H, d, J = 8.1 Hz), 7.96-8.04 (2H, m), 8.11-8.28 (2H, m), 8.39 (3H, brs), 9.34 (1H, s), 10.50 (1H, brs).

Example 242

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-

methylphenyl)pyridin-3-yl]-2,5-dimethylfuran-3-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-2,5-dimethylfuran-3-carboxamide dihydrochloride (215 mg, yield 90%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 2,5-dimethylfuran-3-carbonyl chloride (119 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.17 (3H, s), 2.17-2.29 (1H, m), 2.29 (3H, s), 2.34 (3H, s), 2.54 (3H, s), 2.99 (2H, brs), 3.82 (2H, d, J = 5.1 Hz), 6.25 (1H, s), 7.20 (2H, d, J = 8.1 Hz), 7.26 (2H, d, J = 8.1 Hz), 8.28 (3H, brs), 9.32 (1H, brs).

Example 243

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-methylthiophene-2-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-methylthiophene-2-carboxamide dihydrochloride (215 mg, yield 90%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 3-methylthiophene-2-carbonyl chloride (120 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.08 (3H, s), 2.09-2.33 (1H, m), 2.34 (3H, s), 2.51 (3H, s), 2.91 (2H, brs), 3.82 (2H, brs), 6.89 (1H, d, J = 5.1 Hz), 7.19 (2H, d, J = 7.8 Hz), 7.27 (2H, d, J = 7.8 Hz), 7.55 (1H, d, J = 5.1 Hz), 8.17 (3H, brs), 9.37 (1H, brs).

Example 244

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-1-benzothiophene-2-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-1-benzothiophene-2-carboxamide dihydrochloride (215 mg, yield 90%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 1-benzothiophene-2-carbonyl chloride (150 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.20-2.28 (1H, m), 2.28 (3H, s), 2.60 (3H, s), 3.00 (2H, brs), 3.84 (2H, d, J = 5.4 Hz), 7.25 (4H, s), 7.41-7.50 (2H, m), 7.91 (1H, d, J = 6.9 Hz), 8.00 (1H, d, J = 6.9 Hz), 8.04 (1H, s), 8.33 (3H, brs), 10.34 (1H, brs).

Example 245

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-methyl-1-benzofuran-2-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-methyl-1-benzofuran-2-carboxamide dihydrochloride (213 mg, yield 90%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 3-methyl-1-benzofuran-2-carbonyl chloride (150 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.16-2.29 (1H, m), 2.29 (3H, s), 2.41 (3H, s), 2.60 (3H, s), 3.03 (2H, brs), 3.83 (2H, brs), 7.25 (4H, s), 7.35 (1H, t, J = 6.9 Hz), 7.49 (1H, t, J = 6.9 Hz), 7.56 (1H, d, J = 6.9 Hz), 7.73 (1H, d, J = 6.9 Hz), 8.35 (3H, brs), 10.08 (1H, brs).

Example 246

methyl [4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)-2-oxopiperazin-1-yl]acetate dihydrochloride

1) Methyl [4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-

isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)-2-oxopiperazin-1-yl]acetate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and methyl (2-oxopiperazin-1-yl)acetate (344 mg, 2.0 mmol) according to a method similar to the method of Example 95-1).
EIMS(M+1):582

2) Methyl [4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)-2-oxopiperazin-1-yl]acetate dihydrochloride (271 mg, yield 49%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).
^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.3 Hz), 1.99-2.28 (1H, m), 2.37 (3H, s), 2.50 (3H, s), 2.60 (2H, brs), 3.14 (2H, t, J = 5.1 Hz), 3.46 (2H, t, J = 5.1 Hz), 3.66 (3H, s), 3.81 (4H, brs), 4.08 (2H, s), 7.17 (2H, d, J = 7.8 Hz), 7.29 (2H, d, J = 7.8 Hz), 8.43 (3H, brs).

Example 247

[5-(methoxycarbonyl)pyridin-2-yl]methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate

1) To a solution of 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.85 g, 4.48 mmol), methyl 6-(hydroxymethyl)nicotinate (0.68 g, 4.07 mmol) and triphenylphosphine (1.39 g, 5.29 mmol) in tetrahydrofuran (20 mL) was added 40% diethyl azodicarboxylate toluene solution (2.3 mL, 5.29 mmol) and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give [5-(methoxycarbonyl)pyridin-2-yl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (2.29 g, yield 99%) as a white solid.
^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.17-2.26 (1H, m), 2.35 (3H, s), 2.58 (3H, s), 2.79 (2H, d, J = 7.2

Hz), 3.96 (3H, s), 4.13-4.15 (2H, m), 4.21 (1H, brs), 5.11 (2H, s), 6.88 (1H, d, J = 8.5 Hz), 7.06 (2H, d, J = 8.1 Hz), 7.13 (2H, d, J = 7.9 Hz), 8.14 (1H, dd, J = 8.2, 2.2 Hz), 9.10 (1H, dd, J = 2.1, 0.75 Hz).

2) [5-(Methoxycarbonyl)pyridin-2-yl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.37 g, 0.659 mmol) was dissolved in 4N hydrogen chloride ethyl acetate solution (10 mL) and the mixture was stirred at room temperature for 30 min. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to give [5-(methoxycarbonyl)pyridin-2-yl]methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (142 mg, yield 46%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 2.17-2.29 (1H, m), 2.35 (3H, s), 2.57 (3H, s), 2.81 (2H, d, J = 7.4 Hz), 3.65 (2H, s), 3.96 (3H, s), 5.11 (2H, s), 6.89 (1H, d, J = 8.3 Hz), 7.10-7.16 (4H, m), 8.14 (1H, dd, J = 8.2, 2.2 Hz), 9.10 (1H, d, J = 1.3 Hz).

Example 248

6-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]nicotinic acid trihydrochloride

1) 6-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]nicotinic acid (1.08 g, yield 58%) was obtained as a colorless oil from [5-(methoxycarbonyl)pyridin-2-yl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.90 g, 3.38 mmol) according to a method similar to the method of Exampl 9-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.27-2.35 (4H, m), 2.60 (3H, s), 2.81 (2H, d, J = 7.2 Hz), 4.14-4.15

(2H, m), 4.25 (1H, brs), 5.14 (2H, s), 6.88-6.95 (1H, m), 7.06-7.19 (4H, m), 8.19 (1H, dd, J = 8.2, 2.2 Hz), 9.16 (1H, s).

2) 6-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]nicotinic acid trihydrochloride (413 mg, yield 81%) was obtained as a white solid from 6-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]nicotinic acid (0.50 g, 0.913 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 2.18-2.28 (1H, m), 2.33 (3H, s), 2.63 (3H, brs), 2.90-2.97 (2H, m), 3.82 (2H, d, J = 5.1 Hz), 5.15 (2H, s), 7.03 (1H, d, J = 8.1 Hz), 7.17-7.23 (4H, m), 8.17 (1H, dd, J = 8.2, 2.0 Hz), 8.38 (3H, brs), 8.98 (1H, d, J = 1.5 Hz).

Example 249

[5-(aminocarbonyl)pyridin-2-yl]methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate

1) [5-(Aminocarbonyl)pyridin-2-yl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (222 mg, yield 38%) was obtained as a colorless oil from 6-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]nicotinic acid (0.58 g, 1.06 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.17-2.26 (1H, m), 2.36 (3H, s), 2.58 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 4.13-4.15 (2H, m), 4.22 (1H, brs), 5.10 (2H, s), 6.92 (1H, d, J = 7.9 Hz), 7.07 (2H, d, J = 8.1 Hz), 7.14 (2H, d, J = 7.9 Hz), 8.03 (1H, dd, J = 8.3, 2.3 Hz), 8.89 (1H, d, J = 2.3 Hz).

2) [5-(Aminocarbonyl)pyridin-2-yl]methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (159 mg, yield 87%) was obtained as a colorless oil from [5-(aminocarbonyl)pyridin-2-yl]methyl 5-{[(tert-

butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.22 g, 0.406 mmol) according to a method similar to the method of Example 247-2).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 2.15-2.31 (1H, m), 2.36 (3H, s), 2.57 (3H, s), 2.81 (2H, d, J = 7.4 Hz), 3.65 (2H, s), 5.10 (2H, s), 6.94 (1H, d, J = 7.7 Hz), 7.11-7.17 (4H, m), 8.03 (1H, dd, J = 8.1, 2.3 Hz), 8.89 (1H, d, J = 2.3 Hz).

Example 250

ethyl 4-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-ethylpyrimidine-5-carboxylate tetrahydrochloride

1) Ethyl 4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-ethylpyrimidine-5-carboxylate (308 mg, yield 40%) was obtained as a white solid from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.53 g, 1.33 mmol) and ethyl 2-ethyl-4-hydroxypyrimidine-5-carboxylate (0.26 g, 1.33 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.8 Hz), 1.20-1.29 (6H, m), 1.39 (9H, s), 2.19-2.28 (1H, m), 2.34 (3H, s), 2.67 (3H, s), 2.75-2.83 (4H, m), 4.10 (2H, d, J = 4.9 Hz), 4.27-4.34 (3H, m), 5.22 (2H, s), 7.06 (2H, d, J = 8.1 Hz), 7.14 (2H, d, J = 7.9 Hz), 8.86 (1H, s).

2) Ethyl 4-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-ethylpyrimidine-5-carboxylate tetrahydrochloride (269 mg, yield 80%) was obtained as a white solid from ethyl 4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-ethylpyrimidine-5-carboxylate (308 mg, 0.536 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 1.19 (3H, t, J = 7.5 Hz), 1.25 (3H, t, J = 7.1 Hz), 2.14-2.23 (1H, m), 2.43 (3H,

s), 2.58-2.67 (2H, m), 2.81-2.97 (3H, m), 3.13 (2H, brs), 3.73-3.83 (2H, m), 4.22 (2H, t, J = 7.0 Hz), 4.42 (2H, s), 7.25-7.31 (2H, m), 7.38-7.43 (2H, m), 8.43 (3H, brs), 8.46 (1H, s).

Example 251

4-(1H-tetrazol-5-yl)benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) A solution of 4-cyanobenzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.28 g, 2.43 mmol) and tributyltin azide (2.3 mL, 8.49 mmol) in toluene (7.5 mL) was heated under reflux under an argon atmosphere for 3 hrs. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give 4-(1H-tetrazol-5-yl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.23 g, yield 88%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.15-2.24 (1H, m), 2.25 (3H, s), 2.54 (3H, s), 2.83 (2H, d, J = 7.2 Hz), 4.18 (2H, d, J = 4.9 Hz), 4.32 (1H, brs), 5.00 (2H, s), 7.01 (2H, d, J = 7.9 Hz), 7.07 (2H, d, J = 7.9 Hz), 7.18 (2H, d, J = 8.1 Hz), 8.03 (2H, d, J = 8.1 Hz).

2) 4-(1H-Tetrazol-5-yl)benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (688 mg, yield 95%) was obtained as a white solid from 4-(1H-tetrazol-5-yl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.75 g, 1.33 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.17-2.26 (1H, m), 2.30 (3H, s), 2.54 (3H, s), 2.87 (2H, d, J = 6.8 Hz), 3.81 (2H, d, J = 5.5 Hz), 5.08 (2H, s), 7.14-7.25 (6H, m), 8.02 (2H, d, J = 8.1 Hz), 8.22 (3H, brs).

Example 252

5-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]furan-2-

carboxylic acid dihydrochloride

1) [5-(Methoxycarbonyl)-2-furyl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (2.37 g, yield 88%) was obtained as a yellow oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (2.00 g, 4.85 mmol) and methyl 5-(chloromethyl)furan-2-carboxylate (0.85 g, 4.85 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.13-2.24 (1H, m), 2.35 (3H, s), 2.52 (3H, s), 2.77 (2H, d, J = 7.2 Hz), 3.91 (3H, s), 4.11 (2H, d, J = 5.1 Hz), 4.19 (1H, brs), 4.94 (2H, s), 6.24 (1H, d, J = 3.6 Hz), 7.00 (2H, d, J = 8.1 Hz), 7.06 (1H, d, J = 3.6 Hz), 7.11 (2H, d, J = 7.9 Hz).

2) 5-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]furan-2-carboxylic acid (1.95 g, yield 95%) was obtained as a white solid from [5-(methoxycarbonyl)-2-furyl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (2.11 g, 3.83 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.14-2.25 (1H, m), 2.36 (3H, s), 2.53 (3H, s), 2.86 (2H, d, J = 7.0 Hz), 4.09-4.18 (2H, m), 4.26 (1H, brs), 4.99 (2H, s), 6.32 (1H, d, J = 3.4 Hz), 7.03 (2H, d, J = 8.1 Hz), 7.10-7.18 (3H, m).

3) 5-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]furan-2-carboxylic acid dihydrochloride (460 mg, yield 79%) was obtained as a white solid from 5-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]furan-2-carboxylic acid (0.61 g, 1.14 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.16-2.27 (1H, m),

2.33 (3H, s), 2.90 (2H, brs), 3.80 (2H, d, J = 5.3 Hz), 5.05 (2H, s), 6.46 (1H, d, J = 3.4 Hz), 7.11-7.14 (3H, m), 7.17 (2H, d, J = 8.1 Hz), 8.29 (3H, brs).

Example 253

[5-(aminocarbonyl)-2-furyl]methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) [5-(Aminocarbonyl)-2-furyl]methyl 5-({[(tert-butoxycarbonyl)amino]methyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (520 mg, yield 69%) was obtained as a colorless oil from 5-[({[5-({[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-furan-2-carboxylic acid (0.75 g, 1.40 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.14-2.27 (1H, m), 2.35 (3H, s), 2.52 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 4.06-4.13 (2H, m), 4.19 (1H, brs), 4.94 (2H, s), 5.45 (1H, brs), 6.16 (1H, brs), 6.27 (1H, d, J = 3.4 Hz), 6.98 (2H, d, J = 8.1 Hz), 7.04 (1H, d, J = 3.6 Hz), 7.09 (2H, d, J = 7.9 Hz).

2) [5-(Aminocarbonyl)-2-furyl]methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochl ride (471 mg, yield 95%) was obtained as a white solid from [5-(aminocarbonyl)-2-furyl]methyl 5-({[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.52 g, 0.971 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.14-2.27 (1H, m), 2.34 (3H, s), 2.88 (2H, brs), 3.80 (2H, d, J = 5.5 Hz), 5.02 (2H, s), 6.39 (2H, d, J = 3.4 Hz), 7.06 (1H, d, J = 3.4 Hz), 7.12 (2H, d, J = 7.9 Hz), 7.18 (2H, d, J = 8.3 Hz), 7.43 (1H, brs), 7.73 (1H, brs), 8.28 (3H, brs).

Example 254

methyl 3-{[[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl](methyl)amino]carbonyl}benzoate

dihydrochloride

To a mixture of 3-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoic acid (212 mg, 0.4 mmol), potassium carbonate (138 mg, 1.0 mmol) and N,N-dimethylformamide (5 mL) was added methyl iodide (282 mg, 2.0 mmol) and the mixture was stirred at room temperature for 8 hrs. 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. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give an oil. To a solution of the obtained oil in ethyl acetate (1 mL) was added a 4N hydrogen chloride ethyl acetate solution (1 mL) and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from hexane to give methyl 3-{[[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl](methyl)amino]carbonyl}benzoate dihydrochloride (203 mg, yield 95%) as a white powder.

EIMS(M+1):460

Example 255

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]isophthalamide dihydrochloride

1) tert-Butyl {[5-{[3-(aminocarbonyl)benzoyl]amino}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (248 mg, yield 98%) was obtained as a white powder from 3-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoic acid (260 mg, 0.48 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.20-2.31 (1H, m), 2.33 (3H, s), 2.49 (3H, s), 2.78 (2H, brs), 4.13 (2H, brs), 4.40 (1H, brs), 5.79 (1H, brs), 6.38 (1H, brs), 7.03

(2H, d, J = 8.1 Hz), 7.18 (2H, d, J = 8.1 Hz), 7.7.39-7.45 (1H, brs), 7.60-7.63 (1H, m), 7.88-7.92 (2H, m).

2) N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]isophthalamide dihydrochloride (233 mg, yield 99%) was obtained as a white powder from tert-butyl {[5-{[3-(aminocarbonyl)benzoyl]amino}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (248 mg, 0.47 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.3 Hz), 2.22-2.30 (1H, m), 2.30 (3H, s), 2.51 (3H, s), 2.89 (2H, brs), 3.84 (2H, brs), 7.23 (4H, s), 7.56 (1H, t, J = 7.8 Hz), 7.83 (2H, d, J = 7.8 Hz), 8.06 (2H, d, J = 7.8 Hz), 8.14 (1H, s), 8.16 (3H, brs), 10.04 (1H, brs).

Example 256

4-[2-oxo-2-(2-oxo-2-phenylethoxy)ethyl]benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) 4-[2-Oxo-2-(2-oxo-2-phenylethoxy)ethyl]benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (2.85 g, yield 86%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (2.00 g, 4.85 mmol) and phenacyl 4-(bromomethyl)phenylacetate (1.69 g, 4.85 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.15-2.24 (1H, m), 2.38 (3H, s), 2.52 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.82 (2H, s), 4.11-4.16 (2H, m), 4.21 (1H, brs), 4.91 (2H, s), 5.36 (2H, s), 7.02-7.05 (4H, m), 7.15 (2H, d, J = 7.7 Hz), 7.26-7.29 (2H, m), 7.46-7.51 (2H, m), 7.58-7.64 (1H, m), 7.88-7.91 (2H, m).

2) 4-[2-Oxo-2-(2-oxo-2-phenylethoxy)ethyl]benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (117 mg, yield 45%) was obtained as a white

solid from 4-[2-oxo-2-(2-oxo-2-phenylethoxy)ethyl]benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.27 g, 0.398 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.16-2.27 (1H, m), 2.38 (3H, s), 2.83 (2H, brs), 3.81 (2H, d, J = 5.3 Hz), 3.85 (2H, s), 4.95 (2H, s), 5.53 (2H, s), 7.02 (2H, d, J = 8.1 Hz), 7.15 (2H, d, J = 7.5 Hz), 7.26 (4H, t, J = 7.72), 7.56 (2H, d, J = 7.9 Hz), 7.67-7.72 (1H, m), 7.92-7.98 (2H, m), 8.17 (3H, brs).

Example 257

4-(2-methoxy-2-oxoethyl)benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) {4-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phenyl}acetic acid (1.65 g, yield 77%) was obtained as a colorless oil from 4-[2-oxo-2-(2-oxo-2-phenylethoxy)ethyl]benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (2.58 g, 3.80 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.95 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.14-2.23 (1H, m), 2.37 (3H, s), 2.52 (3H, s), 2.77 (2H, d, J = 7.2 Hz), 3.65 (2H, s), 4.09-4.16 (2H, m), 4.21 (1H, brs), 4.90 (2H, s), 7.00-7.06 (4H, m), 7.13 (2H, d, J = 7.9 Hz), 7.21 (2H, d, J = 8.1 Hz).

2) To a mixture of {4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phenyl}acetic acid (0.65 g, 1.16 mmol), potassium carbonate (0.32 g, 2.32 mmol) and N,N-dimethylformamide (15 mL) was added methyl iodide (197 mg, 1.39 mmol) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated brine and dried over

anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give 4-(2-methoxy-2-oxoethyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.56 g, yield 84%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.13-2.26 (1H, m), 2.38 (3H, s), 2.52 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.62 (2H, s), 3.70 (3H, s), 4.12-4.13 (2H, m), 4.20 (1H, brs), 4.90 (2H, s), 7.01-7.04 (4H, m), 7.14 (2H, d, J = 7.9 Hz), 7.20 (2H, d, J = 8.1 Hz).

3) 4-(2-Methoxy-2-oxoethyl)benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (483 mg, yield 90%) was obtained as a white solid from 4-(2-methoxy-2-oxoethyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.56 g, 0.974 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.95 (6H, d, J = 6.6 Hz), 2.14-2.26 (1H, m), 2.37 (3H, s), 2.79-2.88 (2H, m), 3.62 (3H, s), 3.69 (2H, s), 3.81 (2H, d, J = 5.3 Hz), 4.94 (2H, s), 7.00 (2H, d, J = 8.1 Hz), 7.13-7.24 (6H, m), 8.21 (3H, brs).

Example 258

{4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phenyl}acetic acid dihydrochloride

{4-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phenyl}acetic acid dihydrochloride (348 mg, yield 73%) was obtained as a white solid from {4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phenyl}acetic acid (0.50 g, 0.892 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.16-2.27 (1H, m),

2.37 (3H, s), 2.53 (3H, s), 2.90 (2H, d, J = 5.8 Hz), 3.57 (2H, s), 3.82 (2H, d, J = 5.3 Hz), 4.95 (2H, s), 6.99 (2H, d, J = 8.1 Hz), 7.15 (2H, d, J = 8.1 Hz), 7.20 (2H, d, J = 8.1 Hz), 7.23 (2H, d, J = 8.1 Hz), 8.30 (3H, brs).

Example 259

4-(2-amino-2-oxoethyl)benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) 4-(2-Amino-2-oxoethyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (360 mg, yield 72%) was obtained as a colorless oil from {4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phenyl}acetic acid (0.50 g, 0.892 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.95 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.13-2.26 (1H, m), 2.39 (3H, s), 2.52 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.58 (2H, s), 4.12-4.13 (2H, m), 4.21 (1H, brs), 4.91 (2H, s), 5.31 (2H, brs), 7.04-7.06 (4H, m), 7.16 (2H, d, J = 7.9 Hz), 7.20 (2H, d, J = 8.1 Hz).

2) 4-(2-Amino-2-oxoethyl)benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (231 mg, yield 67%) was obtained as a white solid from 4-(2-amino-2-oxoethyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.36 g, 0.643 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.95 (6H, d, J = 6.6 Hz), 2.14-2.25 (1H, m), 2.38 (3H, s), 2.86 (2H, brs), 3.37 (2H, s), 3.81 (2H, d, J = 5.5 Hz), 4.93 (2H, s), 6.88 (1H, brs), 6.98 (2H, d, J = 8.1 Hz), 7.13-7.25 (6H, m), 7.49 (1H, brs), 8.21 (3H, brs).

Example 260

4-(methylsulfonyl)benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydr chloride

1) 4-(Methylsulfonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (530 mg, yield 73%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (495 mg, 1.20 mmol) and 1-(bromomethyl)-4-(methylsulfonyl)benzene (300 mg, 1.20 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.19-2.28 (1H, m), 2.38 (3H, s), 2.55 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 3.04 (3H, s), 4.12-4.13 (2H, m), 4.21 (1H, brs), 5.01 (2H, s), 7.04 (2H, d, J = 8.1 Hz), 7.14 (2H, d, J = 7.9 Hz), 7.19 (2H, d, J = 8.3 Hz), 7.83 (2H, d, J = 8.5 Hz).

2) 4-(Methylsulfonyl)benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (466 mg, yield 92%) was obtained as a white solid from 4-(methylsulfonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.53 g, 0.913 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.15-2.26 (1H, m), 2.36 (3H, s), 2.54-2.58 (3H, m), 2.87-2.97 (2H, m), 3.22 (3H, s), 3.81 (2H, d, J = 5.1 Hz), 5.11 (2H, s), 7.15-7.28 (6H, m), 7.84 (2H, d, J = 8.3 Hz), 8.23-8.40 (3H, m).

Example 261

ethyl 3-[4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)-2-oxopiperazin-1-yl]propionate dihydrochloride

1) Ethyl 3-[4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)-2-oxopiperazin-1-yl]propionate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and ethyl (2-oxopiperazin-1-yl)propionate (250 mg, 2.0

mmol) according to a method similar to the method of Example 95-1).

EIMS(M+1):610

2) Ethyl 3-[4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)-2-oxopiperazin-1-yl]propionate dihydrochloride (278 mg, yield 49%) was obtained as a white powder from the oil obtained in aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.3 Hz), 1.19 (3H, t, J = 7.2 Hz), 2.14-2.23 (1H, m), 2.37 (3H, s), 2.64 (2H, s), 3.06 (4H, brs), 3.37-3.47 (4H, m), 3.74 (2H, s), 3.83 (2H, brs), 4.06 (2H, q, J = 7.2 Hz), 7.18 (2H, d, J = 7.8 Hz), 7.29 (2H, d, J = 7.8 Hz), 8.40 (3H, brs).

Example 262

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-2-methoxybenzamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-2-methoxybenzamide dihydrochloride (209 mg, yield 95%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 2-methoxybenzoyl chloride (128 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.18-2.29 (1H, m), 2.36 (3H, s), 2.61 (3H, s), 3.03 (2H, s), 3.69 (3H, s), 3.84 (2H, brs), 6.98 (1H, t, J = 7.5 Hz), 7.08 (1H, d, J = 8.1 Hz), 7.24 (2H, d, J = 8.1 Hz), 7.32 (2H, d, J = 8.1 Hz), 7.39-7.49(2H, m), 8.32 (3H, brs), 9.55 (1H, brs).

Example 263

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-2-fluorobenzamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-2-fluorobenzamide dihydrochloride (204 mg, yield 95%) was obtained as a white powder from tert-

butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 2-fluorobenzoyl chloride (122 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.21-2.28 (1H, m), 2.37 (3H, s), 2.55 (3H, s), 2.92 (2H, s), 3.84 (2H, s), 7.13-7.32 (7H, m), 7.49-7.54 (1H, m), 8.20 (3H, brs), 9.86 (1H, brs).

Example 264

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-methoxybenzamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-methoxybenzamide dihydrochloride (196 mg, yield 80%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 3-methoxybenzoyl chloride (128 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.19-2.31 (1H, m), 2.32 (3H, s), 2.58 (3H, s), 3.02 (2H, s), 3.75 (3H, s), 3.85 (2H, brs), 7.08-7.10 (2H, m), 7.18-7.36 (6H, m), 8.33 (3H, brs), 9.96 (1H, brs).

Example 265

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-fluorobenzamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-fluorobenzamide dihydrochloride (186 mg, yield 78%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 3-fluorobenzoyl chloride (122 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :1.01 (6H, d, J = 6.6 Hz), 2.18-2.36 (1H, m), 2.31 (3H, s), 2.62 (3H, s), 3.08 (2H, s), 3.86 (2H, s), 7.26

(4H, s), 7.38-7.42 (2H, m), 7.50 (2H, s), 8.41 (3H, brs), 10.22 (1H, brs).

Example 266

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-methoxybenzamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-methoxybenzamide dihydrochloride (209 mg, yield 95%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 4-methoxybenzoyl chloride (128 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.19-2.26 (1H, m), 2.31 (3H, s), 2.63 (3H, s), 3.12 (2H, s), 3.79 (3H, s), 3.87 (2H, brs), 6.96 (1H, t, J = 9.0 Hz), 7.25 (4H, s), 7.67 (2H, d, J = 9.0 Hz), 8.43 (3H, brs), 9.92 (1H, brs).

Example 267

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-fluorobenzamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-fluorobenzamide dihydrochloride (204 mg, yield 95%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 4-fluorobenzoyl chloride (122 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.14-2.31 (1H, m), 2.31 (3H, s), 2.62 (3H, s), 3.08 (2H, s), 3.85 (2H, s), 7.25-7.30 (6H, m), 7.70-7.75 (2H, m), 8.41 (3H, brs), 10.14 (1H, brs).

Example 268

(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate dihydrochloride

1) (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate (540 mg, yield 86%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (500 mg, 1.17 mmol) and 4-(chloromethyl)-5-methyl-1,3-dioxol-2-one (209 mg, 1.41 mmol) according to a method similar to the method of Example 176-1).
^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8 Hz), 1.38 (9H, s), 2.14 (3H, s), 2.16-2.28 (1H, m), 2.40 (3H, s), 2.49 (3H, s), 2.75 (2H, d, J = 7.4 Hz), 3.40 (2H, s), 4.04 (2H, d, J = 5.1 Hz), 4.21 (1H, brs), 4.76 (2H, s), 6.93 (2H, d, J = 7.9 Hz), 7.21 (2H, d, J = 7.9 Hz).

2) (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate dihydrochloride (500 mg, yield 99%) was obtained as a white powder from (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate (530 mg, 0.984 mmol) according to a method similar to the method of Example 2-3).
^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.15 (3H, s), 2.18-2.25 (1H, m), 2.39 (3H, s), 2.88 (3H, s), 3.29 (2H, d, J = 7.2 Hz), 3.54-3.64 (4H, m), 4.94 (2H, s), 7.16 (2H, d, J = 7.9 Hz), 7.33 (2H, d, J = 7.9 Hz), 8.63 (3H, brs).

Example 269

2-[4-(methoxycarbonyl)phenyl]ethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) 2-[4-(Methoxycarbonyl)phenyl]ethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.77 g, yield 70%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.80 g, 4.37 mmol) and methyl 4-(2-bromoethyl)benzoate (1.06 g, 4.37 mmol) according to a method similar to the method of Example

169-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.16-2.28 (1H, m), 2.37 (3H, s), 2.46 (3H, s), 2.66 (2H, t, J = 7.0 Hz), 2.77 (2H, d, J = 7.4 Hz), 3.91 (3H, s), 4.11-4.15 (4H, m), 4.22 (1H, brs), 7.02 (2H, d, J = 8.1 Hz), 7.15 (4H, d, J = 8.3 Hz), 7.95 (2H, d, J = 8.5 Hz).

2) 2-[4-(Methoxycarbonyl)phenyl]ethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (291 mg, yield 82%) was obtained as a white solid from 2-[4-(methoxycarbonyl)phenyl]ethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.37 g, 0.644 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.8 Hz), 2.14-2.27 (1H, m), 2.35 (3H, s), 2.42 (3H, brs), 2.73 (2H, d, J = 6.4 Hz), 2.91 (2H, brs), 3.81 (2H, d, J = 5.3 Hz), 3.85 (3H, s), 4.17 (2H, t, J = 6.5 Hz), 7.12 (2H, d, J = 6.8 Hz), 7.22 (2H, d, J = 7.9 Hz), 7.29 (2H, d, J = 8.3 Hz), 7.89 (2H, d, J = 8.3 Hz), 8.34 (3H, brs).

Example 270

4-[2-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)ethyl]benzoic acid dihydrochloride

1) 4-[2-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)ethyl]benzoic acid (1.30 g, yield 95%) was obtained as a colorless oil from 2-[4-(methoxycarbonyl)phenyl]ethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.40 g, 2.44 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.16-2.27 (1H, m), 2.37 (3H, s), 2.44 (3H, s), 2.70 (2H, d, J = 6.9 Hz), 2.79 (2H, d, J = 7.2 Hz), 4.11-4.18 (4H, m), 4.24 (1H,

brs), 7.02 (2H, d, J = 7.9 Hz), 7.15-7.20 (4H, m), 8.01 (2H, d, J = 8.3 Hz).

2) 4-[2-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)ethyl]benzoic acid dihydrochloride (359 mg, yield 94%) was obtained as a white solid from 4-[2-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)ethyl]benzoic acid (0.40 g, 0.713 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.14-2.25 (1H, m), 2.35 (3H, s), 2.42 (3H, s), 2.71 (2H, t, J = 6.5 Hz), 2.87 (2H, d, J = 7.0 Hz), 3.80 (2H, d, J = 5.3 Hz), 4.16 (2H, t, J = 6.5 Hz), 7.11 (2H, d, J = 8.1 Hz), 7.21-7.26 (4H, m), 7.87 (2H, d, J = 8.1 Hz), 8.28 (3H, brs).

Example 271

2-[4-(aminocarbonyl)phenyl]ethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) 2-[4-(Aminocarbonyl)phenyl]ethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (598 mg, yield 99%) was obtained as a colorless oil from 4-[2-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)ethyl]benzoic acid (0.60 g, 1.07 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.16-2.27 (1H, m), 2.37 (3H, s), 2.47 (3H, s), 2.66 (2H, t, J = 7.1 Hz), 2.78 (2H, d, J = 7.2 Hz), 4.09-4.15 (4H, m), 4.24 (1H, brs), 5.67 (1H, brs), 6.06 (1H, brs), 7.02 (2H, d, J = 7.9 Hz), 7.15-7.19 (4H, m), 7.73 (2H, d, J = 8.1 Hz).

2) 2-[4-(Aminocarbonyl)phenyl]ethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (508 mg, yield 90%) was obtained as a white solid from 2-[4-(aminocarbonyl)phenyl]ethyl 5-{[(tert-

butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (598 mg, 1.06 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.16-2.25 (1H, m), 2.36 (3H, s), 2.42 (3H, brs), 2.67 (2H, t, J = 6.4 Hz), 2.87 (2H, brs), 3.81 (2H, d, J = 5.5 Hz), 4.16 (2H, t, J = 6.5 Hz), 7.11 (2H, d, J = 7.7 Hz), 7.18-7.25 (4H, m), 7.32 (1H, brs), 7.81 (2H, d, J = 8.3 Hz), 7.95 (1H, brs), 8.27 (3H, brs).

Example 272

3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzamide

1) tert-Butyl {[5-{[3-(aminocarbonyl)phenoxy]methyl}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (240 mg, yield 80%) was obtained as a white solid from 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzoic acid (0.30 g, 0.578 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.21-2.28 (1H, m), 2.35 (3H, s), 2.62 (3H, s), 2.79 (2H, d, J = 7.2 Hz), 4.09-4.11 (2H, m), 4.22 (1H, brs), 4.68 (2H, s), 5.55 (1H, brs), 6.01 (1H, brs), 6.96-7.01 (1H, m), 7.04 (2H, d, J = 7.9 Hz), 7.17 (2H, d, J = 7.7 Hz), 7.29-7.32 (2H, m), 8.02 (1H, s).

2) 3-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}benzamide (166 mg, yield 85%) was obtained as a white solid from tert-butyl {[5-{[3-(aminocarbonyl)phenoxy]methyl}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (240 mg, 0.463 mmol) according to a method similar to the method of Example 239-2).

^{1}H-NMR ($CDCl_3$) :1.00 (6H, d, J = 6.8 Hz), 2.21-2.30 (1H, m), 2.36 (3H, s), 2.61 (3H, s), 2.81 (2H, d, J = 7.2 Hz), 3.60 (2H, s), 4.68 (2H, s), 5.52 (1H, brs), 6.06 (1H, brs), 6.96-7.00 (1H, m), 7.09 (2H, d, J = 7.9 Hz), 7.18 (2H, d, J = 7.9 Hz), 7.25-7.31 (3H, m).

Example 273

methyl 2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methylbenzoate dihydrochloride

1) Methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methylbenzoate (720 mg, yield 52%) was obtained as a white powder from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.0 g, 2.51 mmol) and methyl 2-hydroxy-5-methylbenzoate (500 mg, 3.01 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.17-2.26 (1H, m), 2.27 (3H, s), 2.37 (3H, s), 2.67 (3H, s), 2.78 (2H, d, J = 7.2 Hz), 3.80 (3H, s), 4.09 (2H, d, J = 4.9 Hz), 4.20 (1H, brs), 4.68 (2H, s), 7.02-7.06 (3H, m), 7.11 (1H, dd, J = 8.5, 1.9 Hz), 7.16 (2H, d, J = 7.7 Hz), 7.52 (1H, d, J = 1.9 Hz).

2) Methyl 2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methylbenzoate dihydrochloride (100 mg, yield 70%) was obtained as a white powder from methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methylbenzoate (150 mg, 0.274 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.03 (6H, d, J = 6.2 Hz), 2.18-2.24 (1H, m), 2.24 (3H, s), 2.37 (3H, s), 2.99 (3H, s), 3.29 (2H, d, J = 7.2 Hz), 3.70-3.76 (5H, m), 4.78 (2H, s), 6.78 (1H, d, J = 8.5 Hz), 7.17-7.40 (5H, m), 7.46 (1H, s), 8.63 (3H, brs).

Example 274

methyl 2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-chlorobenzoate dihydrochloride

1) Methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-

chlorobenzoate (0.80 g, yield 71%) was obtained as a white powder from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.80 g, 2.0 mmol) and methyl 5-chlorosalicylate (0.56 g, 3.0 mmol) according to a method similar to the method of Example 106-1).

^{1}H-NMR ($CDCl_3$) : 0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.15-2.30 (1H, m), 2.37 (3H, s), 2.66 (3H, s), 2.78 (2H, d, J = 7.2 Hz), 3.81 (3H, s), 4.09 (2H, d, J = 4.9 Hz), 4.15-4.25 (1H, m), 4.69 (2H, s), 6.57 (1H, d, J = 8.9 Hz), 7.03 (2H, d, J = 8.0 Hz), 7.17 (2H, d, J = 8.0 Hz), 7.26 (1H, dd, J = 2.7, 8.9 Hz), 7.69 (1H, d, J = 2.7 Hz).

2) A mixture of methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-chlorobenzoate (0.19 g, 0.33 mmol) and hydrogen chloride methanol solution (4 mL) was stirred at room temperature for 3 hrs. The reaction mixture was concentrated under reduced pressure and the obtained solid was washed with diisopropyl ether to give methyl 2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-chlorobenzoate dihydrochloride (0.17 g, yield 96%) as a white powder.

^{1}H-NMR (DMSO-d_6) : 0.99 (6H, d, J = 6.6 Hz), 2.15-2.30 (1H, m), 2.35 (3H, s), 3.08 (3H, brs), 3.08 (2H, brs), 3.75 (3H, s), 3.82 (2H, d, J = 4.5 Hz), 4.79 (2H, s), 6.97 (1H, d, J = 9.0 Hz), 7.24 (2H, d, J = 7.9 Hz), 7.29 (2H, d, J = 7.9 Hz), 7.52 (1H, dd, J = 2.8, 9.0 Hz), 7.65 (1H, d, J = 2.8 Hz), 8.35 (3H, brs).

Example 275

methyl 2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methoxybenzoate dihydrochloride

1) Methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methoxybenzoate (0.70 g, yield 62%) was obtained as a white

powder from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.80 g, 2.0 mmol) and methyl 5-methoxysalicylate (0.55 g, 3.0 mmol) according to a method similar to the method of Example 106-1).

^{1}H-NMR ($CDCl_3$) : 0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.15-2.30 (1H, m), 2.38 (3H, s), 2.69 (3H, s), 2.78 (2H, d, J = 7.2 Hz), 3.77 (3H, s), 3.81 (3H, s), 4.09 (2H, d, J = 4.7 Hz), 4.15-4.30 (1H, m), 4.68 (2H, s), 6.50 (1H, d, J = 9.0 Hz), 6.85 (1H, dd, J = 3.2, 9.0 Hz), 7.01 (2H, d, J = 7.9 Hz), 7.17 (2H, d, J = 7.9 Hz), 7.24 (1H, d, J = 3.2 Hz).

2) Methyl 2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methoxybenzoate dihydrochloride (0.20 g, yield 96%) was obtained as a white powder from methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methoxybenzoate (0.23 g, 0.40 mmol) according to a method similar to the method of Example 274-2).

^{1}H-NMR (DMSO-d_6) : 0.98 (6H, d, J = 6.6 Hz), 2.15-2.30 (1H, m), 2.37 (3H, s), 2.73 (3H, brs), 2.93 (2H, brs), 3.72 (3H, s), 3.73 (3H, s), 3.79 (2H, d, J = 4.9 Hz), 4.69 (2H, brs), 6.77 (1H, d, J = 9.0 Hz), 7.01 (1H, dd, J = 3.2, 9.0 Hz), 7.14 (1H, d, J = 3.2 Hz), 7.20 (2H, d, J = 7.8 Hz), 7.29 (2H, d, J = 7.8 Hz), 8.11 (3H, brs).

Example 276

2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-4-methoxybenzoic acid dihydrochloride

1) Methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-4-methoxybenzoate (0.81 g, yield 72%) was obtained as a white powder from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.80 g, 2.0 mmol) and methyl 4-methoxysalicylate (0.55 g, 3.0 mmol) according to a method similar to the method of Example 106-1).

^{1}H-NMR ($CDCl_3$) : 0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.15-2.30 (1H, m), 2.36 (3H, s), 2.68 (3H, s), 2.78 (2H, d, J = 7.2 Hz), 3.75 (3H, s), 3.77 (3H, s), 4.09 (2H, d, J = 4.7 Hz), 4.20-4.25 (1H, m), 4.68 (2H, s), 6.14 (1H, d, J = 2.4 Hz), 6.48 (1H, dd, J = 2.4, 8.7 Hz), 7.00-7.10 (2H, m), 7.15-7.20 (2H, m), 7.79 (1H, d, J = 8.7 Hz).

2) 2-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-4-methoxybenzoic acid (0.19 g, yield 37%) was obtained as a white powder from methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-4-methoxybenzoate (0.51 g, 0.91 mmol) according to a method similar to the method of Example 36-1).

^{1}H-NMR ($CDCl_3$) : 0.99 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.15-2.35 (1H, m), 2.35 (3H, s), 2.64 (3H, s), 2.81 (2H, d, J = 7.2 Hz), 3.82 (3H, s), 4.09 (2H, d, J = 4.9 Hz), 4.15-4.30 (1H, m), 4.87 (2H, s), 6.30 (1H, d, J = 2.3 Hz), 6.63 (1H, dd, J = 2.3, 8.9 Hz), 7.00 (2H, d, J = 7.9 Hz), 7.18 (2H, d, J = 7.9 Hz), 8.12 (1H, d, J = 8.9 Hz), 10.42 (1H, brs).

3) A mixture of 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-4-methoxybenzoic acid (0.15 g, 0.28 mmol) and 6N hydrochloric acid (4 mL) was stirred at room temperature for 6 hrs. The reaction mixture was concentrated under reduced pressure and the obtained solid was washed with acetonitrile to give 2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-4-methoxybenzoic acid dihydrochloride (0.12 g, yield 81%) as a white powder.

^{1}H-NMR (DMSO-d_6) : 0.99 (6H, d, J = 6.6 Hz), 2.10-2.30 (1H, m), 2.37 (3H, s), 2.86 (3H, brs), 3.06 (2H, brs), 3.73 (3H, s), 3.82 (2H, brs), 4.76 (2H, brs), 6.31 (1H, d, J = 2.1 Hz), 6.60 (1H, dd, J = 2.1, 8.7 Hz), 7.26 (2H, d, J = 7.2 Hz), 7.32 (2H, d, J = 7.2 Hz), 7.68 (1H, d, J = 8.7 Hz), 8.28 (3H, brs).

Example 277

methyl 6-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]meth xy}methyl)nicotinate trihydrochloride

1) A mixture of tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.50 g, 3.76 mmol), triethylamine (1.05 mL, 7.52 mmol) and tetrahydrofuran (50 mL) was cooled to 0 C and methanesulfonyl chloride (647 mg, 5.65 mmol) was added dropwise. After stirring at room temperature for 30 min., the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to give {5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl methanesulfonate as a crude product. The crude product was added to a solution of (5-bromopyridin-2-yl)methanol (848 mg, 4.51 mmol) and sodium hydride (60% in oil, 226 mg, 5.65 mmol) in tetrahydrofuran (50 mL) and the mixture was stirred at 60 C for 1 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give tert-butyl {[5-{[(5-bromopyridin-2-yl)methoxy]methyl}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.35 g, yield 63%) as a white solid.

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.15-2.24 (1H, m), 2.41 (3H, s), 2.65 (3H, s), 2.75 (2H, d, J = 7.4 Hz), 4.06 (2H, d, J = 4.9 Hz), 4.23 (2H, s), 4.39 (2H, s), 7.01 (2H, d, J = 7.9 Hz), 7.16-7.20 (3H, m), 7.73 (1H, dd, J = 8.4, 2.4 Hz), 8.54 (1H, d, J = 2.1 Hz).

2) Methyl 6-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}methyl)nicotinate (1.15 g, yield 88%) was obtained

as a yellow oil from tert-butyl {[5-{[(5-bromopyridin-2-yl)methoxy]methyl}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.35 g, 2.37 mmol) according to a method similar to the method of Example 231-2).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.16-2.25 (1H, m), 2.40 (3H, s), 2.67 (3H, s), 2.76 (2H, d, J = 7.2 Hz), 3.95 (3H, s), 4.06 (2H, d, J = 4.9 Hz), 4.20 (1H, brs), 4.27 (2H, s), 4.50 (2H, s), 7.02 (2H, d, J = 7.9 Hz), 7.19 (2H, d, J = 7.7 Hz), 7.36 (1H, d, J = 8.1 Hz), 8.21 (1H, dd, J = 8.1, 2.1 Hz), 9.08 (1H, d, J = 1.7 Hz).

3) Methyl 6-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}methyl)nicotinate trihydrochloride (114 mg, yield 58%) was obtained as a white solid from methyl 6-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}methyl)nicotinate (0.19 g, 0.347 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.11-2.22 (1H, m), 2.38 (3H, s), 3.14 (2H, brs), 3.81 (2H, d, J = 5.3 Hz), 3.90 (3H, s), 4.29 (2H, s), 4.51 (2H, s), 7.23 (2H, d, J = 7.9 Hz), 7.32 (2H, d, J = 7.9 Hz), 7.38 (1H, d, J = 8.1 Hz), 8.25 (1H, dd, J = 8.1, 2.2 Hz), 8.38 (3H, brs), 8.98 (1H, d, J = 1.5 Hz).

Example 278

6-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}methyl)nicotinic acid trihydrochloride

1) 6-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}methyl)nicotinic acid (760 mg, yield 81%) was obtained as a colorless oil from methyl 6-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}methyl)nicotinate (0.96 g, 1.75 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.14-

2.26 (1H, m), 2.39 (3H, s), 2.71 (3H, s), 2.85 (2H, d, J = 7.2 Hz), 4.05-4.10 (2H, m), 4.29 (3H, brs), 4.52 (2H, s), 7.03 (2H, d, J = 7.9 Hz), 7.38 (1H, d, J = 8.1 Hz), 8.29 (1H, dd, J = 8.2, 1.8 Hz), 9.15 (1H, d, J = 1.5 Hz).

2) 6-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}methyl)nicotinic acid trihydrochloride (259 mg, yield 90%) was obtained as a white solid from 6-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}methyl)nicotinic acid (0.28 g, 0.525 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.4 Hz), 2.11-2.22 (1H, m), 2.39 (3H, s), 2.94 (3H, brs), 3.13-3.22 (2H, m), 3.81 (2H, brs), 4.29 (2H, brs), 4.51 (2H, s), 7.19-7.25 (2H, m), 7.30-7.36 (3H, m), 8.19-8.24 (1H, m), 8.43 (3H, brs), 8.93-8.96 (1H, m).

Example 279

methyl 2-{2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]ethyl}benzoate dihydrochloride

1) To a solution of tert-butyl {[5-formyl-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.36 g, 0.908 mmol) and diethyl (2-bromobenzyl)phosphonate (363 mg, 1.18 mmol) in N,N-dimethylformamide (10 mL) was added sodium methoxide (165 mg, 4.08 mmol) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give tert-butyl {[5-[(E)-2-(2-bromophenyl)vinyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (390 mg, yield 78%) as a white solid.

^{1}H-NMR ($CDCl_3$) :1.00 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.18-2.30 (1H, m), 2.39 (3H, s), 2.72 (3H, s), 2.78 (2H, d, J = 7.4

Hz), 4.11 (2H, d, J = 5.1 Hz), 4.24 (1H, brs), 6.55 (1H, d, J = 16.6 Hz), 6.78 (1H, d, J = 16.6 Hz), 7.02 (2H, d, J = 7.9 Hz), 7.05-7.08 (1H, m), 7.15-7.18 (2H, m), 7.22 (2H, d, J = 7.7 Hz), 7.50 (1H, d, J = 7.5 Hz).

2) Methyl 2-{(E)-2-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]vinyl}benzoate (280 mg, yield 74%) was obtained as a yellow oil from tert-butyl {[5-[(E)-2-(2-bromophenyl)vinyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (390 mg, 0.907 mmol) according to a method similar to the method of Example 231-2).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.18-2.27 (1H, m), 2.39 (3H, s), 2.74 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 3.89 (3H, s), 4.11 (2H, d, J = 5.3 Hz), 4.24 (1H, brs), 6.47 (1H, d, J = 16.8 Hz), 7.02 (2H, d, J = 7.9 Hz), 7.13 (1H, d, J = 7.5 Hz), 7.20-7.29 (4H, m), 7.35-7.40 (1H, m), 7.86 (1H, dd, J = 7.8, 1.4 Hz).

3) A mixture of methyl 2-{(E)-2-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]vinyl}benzoate (0.28 g, 0.53 mmol), 10% palladium-carbon (57 mg, 0.053 mmol) and methanol (10 mL) was stirred in a sealed tube under a 0.5 Mpa hydrogen atmosphere at room temperature for 3 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give methyl 2-{2-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]ethyl}benzoate (250 mg, yield 88%) as a white solid.

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.14-2.23 (1H, m), 2.43 (3H, s), 2.60 (3H, s), 2.62-2.68 (2H, m), 2.73 (2H, d, J = 7.4 Hz), 2.91-2.96 (2H, m), 3.82 (3H, s), 4.01 (2H, d, J = 5.1 Hz), 4.21 (1H, brs), 6.54 (1H, dd, J = 7.4, 1.2 Hz), 6.94 (2H, d, J = 8.1 Hz), 7.15-7.25 (4H, m), 7.77 (1H, dd,

J = 7.6, 1.6 Hz).

4) Methyl 2-{2-[5-(aminomethyl)-6-is butyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl] thyl}benzoate dihydrochloride (201 mg, yield 84%) was obtained as a white solid from methyl 2-{2-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]ethyl}benzoate (0.25 g, 0.471 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.11-2.20 (1H, m), 2.45 (3H, s), 2.63-2.72 (2H, m), 2.83-2.90 (5H, m), 2.91-2.96 (2H, m), 3.18 (2H, brs), 3.73-3.84 (5H, m), 6.65 (1H, d, J = 7.4 Hz), 7.26 (2H, d, J = 7.7 Hz), 7.31 (1H, dd, J = 7.4, 1.4 Hz), 7.35 (1H, dd, J = 7.4, 1.8 Hz), 7.42 (2H, d, J = 7.9 Hz), 7.75 (1H, dd, J = 7.5, 1.5 Hz), 8.46 (3H, brs).

Example 280

methyl 4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}oxy)methyl]benzoate dihydrochloride

1) Methyl 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}oxy)methyl]benzoate (258 mg, yield 64%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (300 mg, 0.703 mmol) and methyl 4-(bromomethyl)benzoate (209 mg, 0.914 mmol) according to a method similar to the method f Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.17-2.26 (1H, m), 2.38 (3H, s), 2.49 (3H, s), 2.77 (2H, d, J = 7.0 Hz), 3.42 (3H, s), 3.93 (3H, s), 4.03 (2H, d, J = 5.1 Hz), 5.09 (2H, s), 6.92 (2H, d, J = 8.1 Hz), 7.16 (2H, d, J = 8.1 Hz), 7.28 (2H, d, J = 8.1 Hz), 8.01 (2H, d, J = 8.1 Hz).

2) Methyl 4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}oxy)methyl]benzoate dihydrochloride (60 mg, yield 92%) was obtained as a white

powder from methyl 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}oxy)methyl]benzoate (68.6 mg, 0.119 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.17-2.23 (1H, m), 2.38 (3H, s), 2.85 (3H, s), 3.25 (2H, d, J = 6.8 Hz), 3.63 (2H, s), 3.79 (2H, d, J = 4.5 Hz), 3.87 (3H, s), 5.13 (2H, s), 7.13 (2H, d, J = 7.9 Hz), 7.30 (2H, d, J = 7.9 Hz), 7.39 (2H, d, J = 8.3 Hz), 7.97 (2H, d, J = 8.3 Hz), 8.63 (3H, brs).

Example 281

2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methylbenzoic acid dihydrochloride

1) 2-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methylbenzoic acid (450 mg, yield 86%) was obtained as a white powder from methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methylbenzoate (537 mg, 0.982 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.18-2.30 (1H, m), 2.32 (3H, s), 2.34 (3H, s), 2.64 (3H, s), 2.80 (2H, d, J = 7.4 Hz), 4.10 (2H, d, J = 4.9 Hz), 4.20 (1H, s), 4.88 (2H, s), 6.72 (1H, d, J = 8.5 Hz), 7.01 (2H, d, J = 8.1 Hz), 7.18 (2H, d, J = 8.1 Hz), 7.23-7.25 (1H, m), 7.97 (1H, d, J = 2.26 Hz).

2) 2-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methylbenzoic acid dihydrochloride (150 mg, yield 94%) was obtained as a white powder from 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methylbenzoic acid (168 mg, 0.316 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.02 (6H, d, J = 6.6 Hz), 2.18-2.30 (1H, m), 2.24 (3H, s), 2.38 (3H, s), 3.00 (3H, s), 3.30 (2H, d, J = 6.8 Hz), 3.87 (2H, d, J = 2.6 Hz), 4.78 (2H, s), 6.72 (1H, d, J = 8.5 Hz), 7.20-7.22 (1H, m), 7.30-7.34 (4H, m), 7.43 (1H, d, J = 1.5 Hz), 8.63 (3H, brs).

Example 282

methyl 3-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}oxy)methyl]benzoate dihydrochloride

1) Methyl 3-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}oxy)methyl]benzoate (401 mg, yield 64%) was obtain d as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (466 mg, 1.09 mmol) and methyl 3-(bromomethyl)benzoate (325 mg, 1.42 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.17-2.26 (1H, m), 2.36 (3H, s), 2.48 (3H, s), 2.74 (2H, d, J = 7.4 Hz), 3.41 (2H, s), 3.93 (3H, s), 4.03 (2H, d, J = 4.9 Hz), 4.20 (1H, brs), 5.08 (2H, s), 6.90-6.93 (2H, m), 7.14 (2H, d, J = 7.7 Hz), 7.40-7.44 (2H, m), 7.93 (1H, d, J = 0.8 Hz), 7.98-8.01 (1H, m).

2) Methyl 3-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}oxy)methyl]benzoate dihydrochloride (80 mg, yield 99%) was obtained as a white powder from methyl 3-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}oxy)methyl]benzoate (84.6 mg, 0.147 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.17-2.26 (1H, m), 2.36 (3H, s), 2.88 (3H, s), 3.30 (2H, d, J = 6.8 Hz), 3.60 (2H, s), 3.80 (2H, d, J = 3.8 Hz), 3.88 (3H, s), 5.13 (2H, s), 7.12

(2H, d, J = 7.9 Hz), 7.27 (2H, d, J = 7.9 Hz), 7.56-7.60 (2H, m), 7.89 (1H, s), 7.95-7.98 (1H, m), 8.63 (3H, brs).

Example 283

2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-4-methoxybenzamide dihydrochloride

1) tert-Butyl {[5-{[2-(aminocarbonyl)-5-methoxyphenoxy]methyl}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.31 g, yield 82%) was obtained as a white powder from 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-4-methoxybenzoic acid (0.38 g, 0.68 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) : 0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.15-2.30 (1H, m), 2.36 (3H, s), 2.63 (3H, s), 2.80 (2H, d, J = 7.2 Hz), 3.80 (3H, s), 4.10 (2H, d, J = 5.1 Hz), 4.20-4.25 (1H, m), 4.75 (2H, s), 5.51 81H, brs), 6.26 (1H, d, J = 2.3 Hz), 6.58 (1H, dd, J = 2.3, 8.9 Hz), 7.00 (2H, d, J = 7.9 Hz), 7.18 (2H, d, J = 7.9 Hz), 7.41 (1H, brs), 8.18 (1H, d, J = 8.9 Hz).

2) 2-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-4-methoxybenzamide dihydrochloride (0.22 g, yield 91%) was obtained as a white powder from tert-butyl {[5-{[2-(aminocarbonyl)-5-methoxyphenoxy]methyl}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.25 g, 0.46 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) : 0.99 (6H, d, J = 6.6 Hz), 2.10-2.30 (1H, m), 2.35 (3H, s), 2.78 (3H, brs), 3.01 (2H, brs), 3.74 (3H, s), 3.80 (2H, d, J = 5.1 Hz), 4.82 (2H, s), 6.42 (1H, d, J = 2.2 Hz), 6.63 (1H, dd, J = 2.2, 8.7 Hz), 7.14 (2H, brs), 7.15-7.35 (4H, m), 7.74 (1H, d, J = 8.7 Hz), 8.28 (3H, brs).

Example 284

methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-naphthoate dihydrochloride

1) Methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-naphthoate (1.07 g, yield 73%) was obtained as a white powder from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.0 g, 2.51 mmol) and methyl 3-hydroxy-2-naphthoate (609 mg, 3.01 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) :1.00 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.18-2.31 (1H, m), 2.34 (3H, s), 2.70 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 3.87 (3H, s), 4.11 (2H, d, J = 4.7 Hz), 4.20 (1H, brs), 4.81 (2H, s), 6.91 (1H, s), 7.09 (2H, d, J = 7.9 Hz), 7.16 (2H, d, J = 7.9 Hz), 7.34-7.38 (1H, m), 7.46-7.50 (1H, m), 7.58-7.62 (1H, m), 7.79 (1H, d, J = 8.1 Hz), 8.22 (1H, s).

2) Methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-naphthoate dihydrochloride (178 mg, yield 84%) was obtained as a white powder from methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-naphthoate (220 mg, 0.378 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.05 (6H, d, J = 6.2 Hz), 2.18-2.33 (1H, m), 2.34 (3H, s), 3.06 (3H, s), 3.36 (2H, d, J = 6.0 Hz), 3.84 (3H, s), 3.91 (2H,s), 4.96 (2H, s), 7.35-7.45 (6H, m), 7.58 (1H, t, J = 7.35 Hz), 7.79 (1H, d, J = 8.1 Hz), 7.98 (1H, d, J = 7.9 Hz), 8.32 (1H, s), 8.63 (3H, brs).

Example 285

3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-naphthoic acid dihydrochloride

1) 3-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-naphthoic acid (860 mg, yield 100%) was obtained as a white powder from methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-naphthoate (817 mg,

1.40 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :1.02 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.20-2.30 (1H, m), 2.32 (3H, s), 2.81 (3H, s), 2.97 (2H, d, J = 6.4 Hz), 4.15 (2H, d, J = 3.0 Hz), 4.20 (1H, brs), 5.01 (2H, s), 7.06 (3H, d, J = 7.7 Hz), 7.18 (2H, d, J = 7.7 Hz), 7.40-7.48 (1H, m), 7.52-7.58 (1H, m), 7.62-7.68 (1H, m), 7.89 (1H, d, J = 8.1 Hz), 8.67 (1H, s).

2) 3-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-naphthoic acid dihydrochloride (300 mg, yield 98%) was obtained as a white powder from 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-naphthoic acid (320 mg, 0.563 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.4 Hz), 2.17-2.29 (1H, m), 2.33 (3H, s), 2.81 (3H, s), 2.90 (2H, s), 3.83 (2H, s), 4.86 (2H, s), 7.24 (1H, s), 7.26-7.33 (4H, m), 7.41 (1H, t, J = 7.5 Hz), 7.53 (1H, t, J = 7.5 Hz), 7.75 (1H, d, J = 8.1 Hz), 7.94 (1H, d, J =8.1 Hz), 8.52 (1H, s), 8.63 (3H, brs).

Example 286

2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methylbenzamide dihydrochloride

1) tert-Butyl {[5-{[2-(aminocarbonyl)-4-methylphenoxy]methyl}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (250 mg, yield 91%) was obtained as a white powder from 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methylbenzoic acid (276 mg, 0.518 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.17-2.28 (1H, m), 2.31 (3H, s), 2.35 (3H, s), 2.64 (3H, s), 2.81 (2H, s), 4.11 (2H, s), 4.20 (1H, s), 4.76 (2H, s), 6.66 (1H, d,

J = 8.5 Hz), 7.00 (2H, d, J = 8.1 Hz), 7.17 (2H, d, J = 8.1 Hz), 7.55 (2H, s), 8.00 (2H, s).

2) 2-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-methylbenzamide dihydrochloride (200 mg, yield 92%) was obtained as a white powder from tert-butyl {[5-{[2-(aminocarbonyl)-4-methylphenoxy]methyl}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (230 mg, 0.433 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.01 (6H, d, J = 6.4 Hz), 2.10-2.30 (4H, m), 2.36 (3H, s), 2.96 (3H, s), 3.27 (2H, d, J = 7.0 Hz), 3.86 (2H, d, J = 4.5 Hz), 4.72-4.84 (2H, m), 6.76 (1H, d, J = 8.5 Hz), 7.15 (1H, dd, J = 8.5, 1.9 Hz), 7.25-7.38 (4H, m), 7.42 (1H, d, J = 1.9 Hz), 8.64 (3H, brs).

Example 287

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetamide dihydrochloride (198 mg, yield 95%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and acetyl chloride (53 L, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 1.76 (3H, s), 2.13-2.22 (1H, m), 2.39 (3H, s), 2.55 (3H, s), 3.02 (2H, brs), 3.82 (2H, s), 7.17 (2H, d, J = 7.5 Hz), 7.33 (2H, d, J = 7.5 Hz), 8.31 (3H, brs), 9.50 (1H, brs).

Example 288

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]propanamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]propanamide dihydrochloride (195 mg, yield 93%) was obtained as a white powder from tert-butyl {[5-

amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and propionyl chloride (65 L, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :0.82 (3H, t, J = 6.9 Hz), 0.98 (6H, d, J = 6.6 Hz), 2.02 (2H, q, J = 6.9 Hz), 2.08-2.32 (1H, m), 2.38 (3H, s), 2.55 (3H, s), 3.06 (2H, brs), 3.83 (2H, s), 7.17 (2H, d, J = 7.8 Hz), 7.32 (2H, d, J = 7.8 Hz), 8.37 (3H, brs), 9.49 (1H, brs).

Example 289

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-2,2-dimethylpropanamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-2,2-dimethylpropanamide dihydrochloride (184 mg, yield 72%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and pivaloyl chloride (92 L, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :0.89 (9H, s), 0.98 (6H, d, J = 6.6 Hz), 2.12-2.24 (1H, m), 2.36 (3H, s), 2.51 (3H, s), 2.97 (2H, brs), 3.81 (2H, s), 7.14 (2H, d, J = 8.1 Hz), 7.28 (2H, d, J = 8.1 Hz), 8.28 (3H, brs), 8.95 (1H, brs).

Example 290

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]cyclopropanecarboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]cyclopropanecarboxamide dihydrochloride (170 mg, yield 85%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and cyclopropanecarbonyl chloride (68 L, 0.75 mmol) according

to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :0.58-0.67 (4H, m), 0.98 (6H, d, J = 6.6 Hz), 1.51-1.58 (1H, m), 2.17-2.26 (1H, m), 2.39 (3H, s), 2.54 (3H, s), 3.02 (2H, brs), 3.81 (2H, s), 7.16 (2H, d, J = 7.5 Hz), 7.32 (2H, d, J = 7.5 Hz), 8.32 (3H, brs), 9.70 (1H, brs).

Example 291

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]cyclopentanecarboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]cyclopentanecarboxamide dihydrochloride (137 mg, yield 62%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and cyclopentanecarbonyl chloride (68 L, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 0.98 (6H, d, J = 6.6 Hz), 1.30-1.62 (9H, m), 2.15-2.24 (1H, m), 2.38 (3H, s), 2.50 (3H, s), 3.02 (2H, brs), 3.81 (2H, s), 7.15 (2H, d, J = 7.8 Hz), 7.30 (2H, d, J = 7.8 Hz), 8.32 (3H, brs), 9.39 (1H, brs).

Example 292

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]pyridine-2-carboxamide trihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]pyridine-2-carboxamide trihydrochloride (218 mg, yield 91%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and pyridine-2-carbonyl chloride (106 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 1.01 (6H, d, J = 6.6 Hz), 2.20-2.28 (1H, m), 2.28 (3H, s), 2.64 (3H, s), 3.14 (2H, brs), 3.86 (2H, s), 7.20-7.27 (4H, m), 7.06-7.65 (1H, m), 7.94-8.02 (2H, m), 8.43

(3H, brs), 8.61 (1H, d, J = 4.8 Hz), 10.33 (1H, s).

Example 293

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]nicotinamide trihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]nicotinamide trihydrochloride (225 mg, yield 94%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and nicotinoyl chloride (106 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 1.02 (6H, d, J = 6.6 Hz), 2.23-2.31 (1H, m), 2.31 (3H, s), 2.73 (3H, s), 3.19 (2H, brs), 3.90 (2H, s), 7.28 (4H, s), 7.73-7.78 (1H, m), 8.35 (2H, d, J = 8.1 Hz), 8.53 (3H, brs), 8.85 (1H, d, J = 3.6 Hz), 8.94 (1H, s), 10.90 (1H, brs).

Example 294

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]isonicotinamide trihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]isonicotinamide trihydrochloride (215 mg, yield 91%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and isonicotinoyl chloride (106 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 1.01 (6H, d, J = 6.6 Hz), 2.22-2.31 (1H, m), 2.31 (3H, s), 2.70 (3H, s), 3.51 (2H, brs), 3.88 (2H, s), 7.28 (4H, s), 7.87 (2H, d, J = 6.0 Hz), 8.51 (3H, brs), 8.88 (2H, d, J = 6.0 Hz), 11.20 (1H, brs).

Example 295

{[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(phenoxymethyl)pyridin-3-yl]methyl}amine dihydrochloride

1) tert-Butyl {[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-

(phenoxymethyl)pyridin-3-yl]methyl}carbamate (270 mg, yield 56%) was obtained as a colorless oil from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.40 g, 1.00 mmol) and phenol (94.5 mg, 1.00 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.18-2.27 (1H, m), 2.36 (3H, s), 2.63 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 4.10 (2H, d, J = 5.7 Hz), 4.22 (1H, brs), 4.62 (2H, s), 6.78-6.82 (2H, m), 6.93 (1H, t, J = 7.4 Hz), 7.05 (2H, d, J = 8.1 Hz), 7.17 (2H, d, J = 7.7 Hz), 7.21-7.24 (2H, m).

2) {[2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-(phenoxymethyl)pyridin-3-yl]methyl}amine dihydrochloride (132 mg, yield 51%) was obtained as a colorless oil from tert-butyl {[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(phenoxymethyl)pyridin-3-yl]methyl}carbamate (0.27 g, 0.569 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.17-2.26 (1H, m), 2.35 (3H, s), 2.82 (3H, brs), 3.12 (2H, brs), 3.83 (2H, d, J = 4.9 Hz), 4.70 (2H, s), 6.85 (2H, d, J = 7.9 Hz), 6.95 (1H, t, J = 7.4 Hz), 7.23-7.33 (6H, m), 8.38 (3H, brs).

Example 296

6-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}methyl)nicotinamide trihydrochloride

1) tert-Butyl {[5-({[5-(aminocarbonyl)pyridin-2-yl]methoxy}methyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (370 mg, yield 77%) was obtained as a white solid from 6-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}methyl)nicotinic acid (0.48 g, 0.899 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.13-2.23 (1H, m), 2.40 (3H, s), 2.67 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 4.07 (2H, d, J = 5.1 Hz), 4.23 (1H, brs), 4.27 (2H, s), 4.49 (2H, s), 7.03 (2H, d, J = 7.9 Hz), 7.20 (2H, d, J = 7.7 Hz), 7.38 (1H, d, J = 7.9 Hz), 8.08 (1H, dd, J = 8.1, 2.3 Hz), 8.90 (1H, d, J = 2.3 Hz).

2) 6-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}methyl)nicotinamide trihydrochloride (282 mg, yield 75%) was obtained as a white solid from tert-butyl {[5-({[5-(aminocarbonyl)pyridin-2-yl]methoxy}methyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.37 g, 0.695 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.11-2.24 (1H, m), 2.39 (3H, s), 2.97 (3H, brs), 3.23 (2H, d, J = 5.8 Hz), 3.82 (2H, d, J = 5.3 Hz), 4.30 (2H, s), 4.52 (2H, s), 7.25 (2H, d, J = 8.1 Hz), 7.32 (2H, d, J = 8.1 Hz), 7.39-7.42 (1H, m), 7.61-7.69 (1H, m), 8.27-8.30 (1H, m), 8.50 (3H, brs), 8.99 (1H, brs).

Example 297

4-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}isophthalic acid dihydrochloride

1) Dimethyl 4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}isophthalate (1.12 g, yield 75%) was obtained as a white solid from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.00 g, 2.51 mmol) and dimethyl 4-hydroxyisophthalate (528 mg, 2.51 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.19-2.31 (1H, m), 2.35 (3H, s), 2.66 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 3.83 (3H, s), 3.89 (3H, s), 4.06-4.11 (2H, m), 4.23 (1H,

brs), 4.77 (2H, s), 6.71 (1H, d, J = 8.9 Hz), 7.05 (2H, d, J = 8.1 Hz), 7.16 (2H, d, J = 7.9 Hz), 8.01 (1H, dd, J = 8.7, 2.3 Hz), 8.41 (1H, d, J = 2.3 Hz).

2) 4-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}isophthalic acid (310 mg, yield 90%) was obtained as a white solid from dimethyl 4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}isophthalate (0.36 g, 0.609 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :1.03 (6H, d, J = 6.4 Hz), 1.37 (9H, s), 2.35 (3H, s), 2.96 (3H, brs), 3.13 (2H, brs), 4.16 (2H, brs), 4.94 (2H, brs), 6.76 (1H, brs), 7.07 (2H, brs), 7.22 (2H, d, J = 7.7 Hz), 8.01 (1H, brs), 8.53 (1H, brs).

3) 4-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}isophthalic acid dihydrochloride (256 mg, yield 86%) was obtained as a white solid from 4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}isophthalic acid (0.31 g, 0.551 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.16-2.28 (1H, m), 2.35 (3H, s), 2.85 (3H, brs), 3.08 (2H, brs), 3.83 (2H, brs), 4.86 (2H, s), 7.01 (1H, d, J = 8.9 Hz), 7.27 (2H, d, J = 8.1 Hz), 7.31 (2H, d, J = 7.7 Hz), 7.97 (1H, dd, J = 8.7, 2.3 Hz), 8.18 (1H, d, J = 2.1 Hz), 8.34 (3H, brs).

Example 298

methyl 2-{(E)-2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]vinyl}benzoate dihydrochloride

Methyl 2-{(E)-2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]vinyl}benzoate dihydrochloride (31.4 mg, yield 33%) was obtained as a white solid from methyl 2-{(E)-2-[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]vinyl}benzoate (0.10 g,

0.189 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.01 (6H, d, J = 6.4 Hz), 2.16-2.28 (1H, m), 2.38 (3H, s), 2.86 (3H, brs), 3.06 (2H, brs), 3.83-3.88 (5H, m), 6.53 (1H, d, J = 16.8 Hz), 7.17 (1H, d, J = 16.8 Hz), 7.24 (2H, d, J = 7.7 Hz), 7.29 (1H, d, J = 7.7 Hz), 7.35 (2H, d, J = 7.9 Hz), 7.40 (1H, t, J = 7.5 Hz), 7.53 (1H, t, J = 7.5 Hz), 7.79 (1H, dd, J = 7.8, 1.2 Hz), 8.32 (3H, brs).

Example 299

4-[1-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)ethyl]benzoic acid dihydrochloride

1) 1-[4-(Methoxycarbonyl)phenyl]ethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.02 g, yield 73%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.00 g, 2.42 mmol) and methyl 4-(1-hydroxyethyl)benzoate (486 mg, 2.42 mmol) according to a method similar to the method of Example 247-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.25 (3H, d, J = 7.0 Hz), 1.39 (9H, s), 2.16-2.24 (1H, m), 2.33 (3H, s), 2.48 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 3.92 (3H, s), 4.11-4.16 (2H, m), 4.22 (1H, brs), 5.73-5.79 (1H, m), 6.96-6.99 (1H, m), 7.04-7.09 (2H, m), 7.13-7.17 (3H, m), 7.93 (2H, d, J = 8.3 Hz).

2) 4-[1-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)ethyl]benzoic acid (950 mg, yield 95%) was obtained as a colorless oil from 1-[4-(methoxycarbonyl)phenyl]ethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.02 g, 1.77 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8 Hz), 1.26 (3H, d, J = 6.8

Hz), 1.39 (9H, s), 2.15-2.26 (1H, m), 2.34 (3H, s), 2.50 (3H, s), 2.79 (2H, d, J = 7.2 Hz), 4.11-4.16 (2H, m), 4.24 (1H, brs), 5.79 (1H, q, J = 6.6 Hz), 7.00-7.13 (4H, m), 7.18 (2H, d, J = 8.1 Hz), 7.99 (2H, d, J = 8.3 Hz).

3) 4-[1-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)ethyl]benzoic acid dihydrochloride (259 mg, yield 93%) was obtained as a white solid from 4-[1-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)ethyl]benzoic acid (0.30 g, 0.522 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.8 Hz), 1.22 (3H, d, J = 6.6 Hz), 2.17-2.26 (1H, m), 2.33 (3H, s), 2.47 (3H, brs), 2.88 (2H, d, J = 5.7 Hz), 3.81 (2H, d, J = 5.5 Hz), 5.76 (1H, q, J = 6.6 Hz), 7.11-7.25 (6H, m), 8.27 (3H, brs).

Example 300

[(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(methylthio)phenoxy]methyl}pyridin-3-yl)methyl]amine dihydrochloride

1) tert-Butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(methylthio)phenoxy]methyl}pyridin-3-yl)methyl]carbamate (1.37 g, yield 70%) was obtained as a colorless oil from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.50 g, 3.76 mmol) and 2-(methylthio)phenol (573 mg, 3.76 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.19-2.31 (1H, m), 2.36 (3H, s), 2.37 (3H, s), 2.69 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 4.09-4.11 (2H, m), 4.21 (1H, brs), 4.68 (2H, s), 6.57 (1H, dd, J = 7.9, 1.3 Hz), 6.91-7.04 (2H, m), 7.06-7.12 (3H, m), 7.17 (2H, d, J = 7.7 Hz).

2) [(2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(methylthio)phenoxy]methyl}pyridin-3-yl)methyl]amine dihydrochloride (112 mg, yield 69%) was obtained as a white

solid from tert-butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(methylthio)phenoxy]methyl}pyridin-3-yl)methyl]carbamate (0.17 mg, 0.326 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.18-2.27 (1H, m), 2.35 (3H, s), 2.36 (3H, s), 2.88 (3H, brs), 3.15 (2H, brs), 3.83 (2H, brs), 4.75 (2H, s), 6.57 (1H, d, J = 6.8 Hz), 6.96-7.07 (2H, m), 7.13-7.16 (1H, m), 7.28 (2H, d, J = 8.3 Hz), 7.32 (2H, d, J = 7.4 Hz), 8.41 (3H, brs).

Example 301

[(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(methylsulfonyl)phenoxy]methyl}pyridin-3-yl)methyl]amine dihydrochloride

1) tert-Butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(methylsulfonyl)phenoxy]methyl}pyridin-3-yl)methyl]carbamate (330 mg, yield 81%) was obtained as a white solid from tert-butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(methylthio)phenoxy]methyl}pyridin-3-yl)methyl]carbamate (0.38 g, 0.730 mmol) according to a method similar to the method of Example 91-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.21-2.30 (1H, m), 2.35 (3H, s), 2.67 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 3.08 (3H, s), 4.11 (2H, d, J = 5.1 Hz), 4.27 (1H, brs), 4.79 (2H, s), 6.76 (1H, d, J = 8.1 Hz), 7.06-7.10 (3H, m), 7.18 (2H, d, J = 7.9 Hz), 7.45-7.50 (1H, m), 7.97 (1H, dd, J = 7.7, 1.7 Hz).

2) [(2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(methylsulfonyl)phenoxy]methyl}pyridin-3-yl)methyl]amine dihydrochloride (227 mg, yield 59%) was obtained as a white solid from tert-butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(methylsulfonyl)phenoxy]methyl}pyridin-3-yl)methyl]carbamate (0:33 g, 0.597 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.4 Hz), 2.17-2.28 (1H, m),

2.35 (3H, s), 2.84 (3H, brs), 3.05-3.17 (5H, m), 3.84 (2H, d, J = 4.7 Hz), 4.87 (2H, s), 7.11 (1H, d, J = 8.3 Hz), 7.18 (1H, t, J = 7.6 Hz), 7.28-7.33 (4H, m), 7.60-7.66 (1H, m), 7.81 (1H, dd, J = 7.7, 1.7 Hz), 8.40 (3H, brs).

Example 302

[(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(methylsulfinyl)phenoxy]methyl}pyridin-3-yl)methyl]amine dihydrochloride

1) To a mixed solution of tert-butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(methylthio)phenoxy]methyl}pyridin-3-yl)methyl]carbamate (0.47 g, 0.902 mmol) in methanol (10 mL) and water (10 mL) was added sodium periodate (377 mg, 1.76 mmol) and the mixture was stirred at room temperature for 2 days. The reaction mixture was diluted with ethyl acetate, washed successively with water and saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give tert-butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(methylsulfinyl)phenoxy]methyl}pyridin-3-yl)methyl]carbamate (164 mg, yield 33%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) :1.00 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.21-2.29 (1H, m), 2.35 (3H, s), 2.61 (3H, s), 2.69 (3H, s), 2.80 (2H, d, J = 7.4 Hz), 4.09-4.11 (2H, m), 4.23 (1H, brs), 4.59 (1H, d, J = 10.0 Hz), 4.83 (1H, d, J = 10.0 Hz), 6.71 (1H, d, J = 8.1 Hz), 6.95-6.98 (1H, m), 7.02-7.05 (1H, m), 7.16-7.21 (3H, m), 7.32-7.38 (1H, m), 7.82 (1H, dd, J = 7.7, 1.7 Hz).

2) [(2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(methylsulfinyl)phenoxy]methyl}pyridin-3-yl)methyl]amine dihydrochloride (97.4 mg, yield 62%) was obtained as a white solid from tert-butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(methylsulfinyl)phenoxy]methyl}pyridin-3-yl)methyl]carbamate (164 mg, 0.306 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.17-2.27 (1H, m), 2.34 (3H, s), 2.63 (3H, s), 2.77 (3H, brs), 3.06 (2H, brs), 3.82 (2H, brs), 4.70 (1H, d, J = 10.6 Hz), 4.90 (1H, d, J = 10.7 Hz), 6.99 (1H, d, J = 8.1 Hz), 7.20-7.33 (5H, m), 7.42-7.47 (1H, m), 7.64 (1H, dd, J = 7.5, 1.7 Hz), 8.31 (3H, brs).

Example 303

3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-naphthamide dihydrochloride

1) tert-Butyl {[5-({[3-(aminocarbonyl)-2-naphthyl]oxy}methyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (230 mg, yield 46%) was obtained as a white powder from 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-naphthoic acid (500 mg, 0.879 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.89 (6H, d, J = 6.6 Hz), 1.35 (9H, s), 2.07-2.22 (1H, m), 2.28 (3H, s), 2.79 (3H, s), 2.87 (2H, d, J = 7.2 Hz), 4.14-4.21 (3H, m), 4.95 (2H, s), 7.04 (1H, s), 7.08-7.21 (4H, m), 7.42-7.52 (1H, m), 7.63 (1H, d, J = 7.5 Hz), 7.74 (1H, d, J = 7.5 Hz), 7.81 (1H, d, J = 8.1 Hz), 8.67 (1H, s), 11.73 (2H, s).

2) 3-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-naphthamide dihydrochloride (200 mg, yield 91%) was obtained as a white powder from tert-butyl {[5-({[3-(aminocarbonyl)-2-naphthyl]oxy}methyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (230 mg, 0.405 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.4 Hz), 2.17-2.30 (1H, m), 2.32 (3H, s), 2.51 (3H, s), 2.81 (2H, s), 3.83 (2H, s), 4.88 (2H, s), 7.25-7.33 (4H, m), 7.40 (1H, t, J = 7.5 Hz), 7.50 (1H, t, J = 7.5 Hz), 7.75 (1H, d, J = 8.1 Hz), 7.92 (1H, d, J =7.9 Hz), 8.12 (1H, s), 8.42 (1H, s), 8.62 (3H, brs).

Example 304

5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)-N-phenylnicotinamide

To a solution of 5-({[(benzyloxy)carbonyl]amino}methyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (523 mg, 1.17 mmol) in tetrahydrofuran (5 mL) was added oxalyl chloride (120 L, 1.4 mmol) and one drop of N,N-dimethylformamide was added. The reaction solution was stirred for 3 hrs. and the reaction mixture was concentrated. The residue was dissolved in tetrahydrofuran (5 mL). Aniline (91 L, 1.0 mmol) and triethylamine (210 L, 1.5 mmol) were added and the mixture was stirred 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. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give an oil. To a solution of the oil in ethanol (5 mL) was added 10% palladium - carbon (50 mg) and the mixture was stirred under a hydrogen atmosphere at room temperature for 3 hrs. The reaction mixture was filtered and the filtrate was concentrated. The obtained oil was crystallized from hexane and diethyl ether to give 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)-N-phenylnicotinamide (320 mg, yield 83%) as a white powder.

^{1}H-NMR ($CDCl_3$) : 1.00 (6H, d, J = 6.6 Hz), 2.17-2.31 (1H, m), 2.34 (3H, s), 2.65 (3H, s), 2.82 (2H, d, J = 7.5 Hz), 3.69 (2H, s), 6.93 (1H, brs), 7.04-7.26 (9H, m).

Example 305

methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate dihydrochloride

1) Ethyl 3-{[5-({[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate (3.23 g, yield 79%) was obtained as a

colorless oil from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (3.00 g, 7.52 mmol) and ethyl 3-hydroxy-1-methyl-1H-pyrazole-4-carboxylate (1.28 g, 7.52 mmol) according to a method similar to the method of Example 183-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.8 Hz), 1.28 (3H, t, J = 7.1 Hz), 1.39 (9H, s), 2.17-2.26 (1H, m), 2.36 (3H, s), 2.66 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.67 (3H, s), 4.08 (2H, d, J = 4.7 Hz), 4.19-4.26 (3H, m), 4.90 (2H, s), 7.10 (2H, d, J = 8.1 Hz), 7.16 (2H, d, J = 8.1 Hz), 7.61 (1H, s).

2) 3-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylic acid (1.58 g, yield 51%) was obtained as a white solid from ethyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate (3.23 g, 5.86 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.8 Hz), 1.38 (9H, s), 2.15-2.28 (1H, m), 2.36 (3H, s), 2.66 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 3.71 (3H, s), 4.04-4.09 (2H, m), 4.23 (1H, brs), 4.98 (2H, s), 7.05 (2H, d, J = 8.1 Hz), 7.19 (2H, d, J = 7.7 Hz), 7.69 (1H, s).

3) 3-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylic acid (0.50 g, 0.957 mmol) was dissolved in N,N-dimethylformamide (5 mL) and methyl iodide (176 mg, 1.24 mmol) and potassium carbonate (0.20 g, 1.44 mmol) were added. The mixture was stirred at room temperature for 1 hr. Ethyl acetate was added to the reaction mixture, and the mixture was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-

isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate (470 mg, yield 91%) as a white solid.

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.17-2.26 (1H, m), 2.36 (3H, s), 2.66 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.68 (3H, s), 3.76 (3H, s), 4.08 (2H, d, J = 4.7 Hz), 4.23 (1H, brs), 4.90 (2H, s), 7.10 (2H, d, J = 7.9 Hz), 7.16 (2H, d, J = 7.9 Hz), 7.62 (1H, s).

4) Methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate dihydrochloride (382 mg, yield 85%) was obtained as a white solid from methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate (0.47 g, 0.876 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.14-2.28 (1H, m), 2.38 (3H, s), 2.90 (3H, brs), 3.16 (2H, brs), 3.65 (3H, s), 3.66 (3H, s), 3.82 (2H, d, J = 5.1 Hz), 4.90 (2H, s), 7.27 (2H, d, J = 8.1 Hz), 7.33 (2H, d, J = 8.1 Hz), 8.09 (1H, s), 8.41 (3H, brs).

Example 306

3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylic acid dihydrochloride

3-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylic acid dihydrochloride (268 mg, yield 94%) was obtained as a white solid from 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylic acid (0.30 g, 0.574 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.4 Hz), 2.14-2.25 (1H, m),

2.39 (3H, s), 2.88 (3H, brs), 3.14 (2H, brs), 3.64 (3H, s), 3.82 (2H, d, J = 4.7 Hz), 4.87 (2H, s), 7.28 (2H, d, J = 7.9 Hz), 7.34 (2H, d, J = 8.1 Hz), 8.00 (1H, s), 8.38 (3H, brs).

Example 307

3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxamide dihydrochloride

1) tert-Butyl {[5-({[4-(aminocarbonyl)-1-methyl-1H-pyrazol-3-yl]oxy}methyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (307 mg, yield 61%) was obtained as a colorless oil from 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylic acid (0.50 g, 0.957 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.19-2.28 (1H, m), 2.37 (3H, s), 2.65 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 3.69 (3H, s), 4.09 (2H, d, J = 4.9 Hz), 4.22 (1H, brs), 4.98 (2H, s), 5.30 (1H, brs), 6.43 (1H, brs), 7.01 (2H, d, J = 8.1 Hz), 7.20 (2H, d, J = 7.7 Hz), 7.69 (1H, s).

2) 3-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxamide dihydrochloride (253 mg, yield 87%) was obtained as a white solid from tert-butyl {[5-({[4-(aminocarbonyl)-1-methyl-1H-pyrazol-3-yl]oxy}methyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (307 mg, 0.588 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.14-2.27 (1H, m), 2.38 (3H, s), 2.93 (3H, brs), 3.17 (2H, brs), 3.63 (3H, s), 3.82 (2H, d, J = 4.7 Hz), 4.93 (2H, s), 6.37 (1H, brs), 7.08 (1H, brs), 7.29 (2H, d, J = 7.9 Hz), 7.35 (2H, d, J = 8.1 Hz), 7.91 (1H, s), 8.42 (3H, brs).

Example 308

(3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazol-4-

yl)acetic acid dihydrochloride

1) To a solution of tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.00 g, 2.51 mmol), methyl (3-hydroxy-1-methyl-1H-pyrazol-4-yl)acetate (0.43 g, 2.51 mmol) and tributylphosphine (0.61 g, 3.01 mmol) in tetrahydrofuran (20 mL) was added 1,1'-(azodicarbonyl)dipiperidine (0.76 g, 3.01 mmol) and the mixture was stirred at room temperature for 30 min. The reaction mixture was filtered and the solvent in the filtrate was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give methyl (3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazol-4-yl)acetate (1.20 g, yield 86%) as a colorless oil. Then, (3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazol-4-yl)acetic acid (173 mg, yield 15%) was obtained as a white solid from methyl (3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazol-4-yl)acetate (1.20 g, 2.18 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.95 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.12-2.30 (1H, m), 2.36 (3H, s), 2.62 (3H, s), 2.80 (2H, d, J = 7.2 Hz), 3.35 (2H, s), 3.66 (3H, s), 4.05-4.09 (2H, m), 4.27 (1H, brs), 4.84 (2H, s), 7.03 (2H, d, J = 7.9 Hz), 7.12 (1H, s), 7.18 (2H, d, J = 7.7 Hz).

2) (3-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazol-4-yl)acetic acid dihydrochloride (84.2 mg, yield 51%) was obtained as a white solid from (3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazol-4-yl)acetic acid (173 mg, 0.323 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.16-2.27 (1H, m), 2.38 (3H, s), 2.76 (3H, brs), 3.00 (2H, brs), 3.15 (2H, s), 3.58 (3H, s), 3.77-3.84 (2H, m), 4.76 (2H, s), 7.23 (2H, d, J = 7.7 Hz), 7.33 (2H, d, J = 7.5 Hz), 7.37 (1H, s), 8.18 (3H, brs).

Example 309

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-(1H-tetrazol-5-yl)benzamide dihydrochloride

To a solution of tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (383 mg, 1.0 mmol) in tetrahydrofuran (5 mL) was added 3-cyanobenzoyl chloride (245 mg, 1.5 mmol) and triethylamine (280 L, 2.0 mmol) was added. The mixture was stirred for 18 hrs. Saturated aqueous sodium hydrogen carbonate solution (5 mL) 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. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give an oil. To a solution of the obtained oil in dimethyl sulfoxide (3 mL) were added sodium azide (97 mg, 1.5 mmol) and ammonium chloride (312 mg, 2.0 mmol) and the mixture was stirred at 100 C for 3 hrs. Distilled water (10 mL) 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. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give an oil. To a solution of the obtained oil in ethyl acetate (2 mL) was added 4N hydrogen chloride ethyl acetate solution (2 mL) and the resulting mixture was stirred at room temperature for 3 hrs. The solvent was evaporated under reduced pressure and the obtained residue was

crystallized from hexane to give N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-(1H-tetrazol-5-yl)benzamide dihydrochloride (86 mg, yield 16%) as a white powder.

^{1}H-NMR (DOSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.11-2.27 (1H, m), 2.27 (3H, s), 2.52 (3H, s), 2.93 (2H, s), 3.83 (2H, s), 7.22 (4H, s), 7.64 (1H, t, J = 7.8 Hz), 7.76 (1H, d, J = 7.8 Hz), 8.16 (4H, brs), 8.34 (1H, brs), 10.10 (1H, brs).

Example 310

methyl 2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methylbenzoate dihydrochloride

1) Methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methylbenzoate (600 mg, yield 44%) was obtained as a white powder from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.0 g, 2.51 mmol) and methyl 2-hydroxy-3-methylbenzoate (500 mg, 3.01 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 1.80 (3H, s), 2.15-2.28 (1H, m), 2.34 (3H, s), 2.70 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.66 (3H, s), 3.97 (2H, d, J = 4.9 Hz), 4.20 (1H, brs), 4.76 (2H, s), 6.52 (2H, d, J = 7.9 Hz), 6.99 (2H, d, J = 7.9 Hz), 7.01-7.06 (1H, m), 7.19 (1H, dd, J = 7.4, 1.0 Hz), 7.44 (1H, dd, J = 7.7, 1.0 Hz).

2) Methyl 2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methylbenzoate dihydrochloride (215 mg, yield 94%) was obtained as a white powder from methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methylbenzoate (240 mg, 0.439 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.01 (6H, d, J = 6.4 Hz), 1.82 (3H, s), 2.14-2.29 (1H, m), 2.36 (3H, s), 3.02 (3H, s), 3.31 (2H, d, J = 6.8

Hz), 3.67 (3H, s), 3.78 (2H, d, J = 2.45 Hz), 4.81 (2H, s), 6.89 (2H, d, J = 7.7 Hz), 7.11-7.20 (3H, m), 7.33 (1H, d, J = 7.0 Hz), 7.43 (1H, d, J = 7.0 Hz), 8.63 (3H, brs).

Example 311

2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N-cyclopropylacetamide dihydrochloride

1) A mixture of [5-({[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (200 mg, 0.469 mmol), cyclopropylamine (80 mg, 1.41 mmol), 1-hydroxy-1H-benzotriazole (215 mg, 1.41 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (270 mg, 0.65 mmol) and N,N-dimethylformamide (5 mL) was stirred at room temperature for 16 hrs. The reaction mixture was diluted with ethyl acetate and washed with saturated brine. The organic layer was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl {[5-[2-(cyclopropylamino)-2-oxoethyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (150 mg, yield 69%) as a white powder.

^{1}H-NMR ($CDCl_3$) :0.33-0.39 (2H, m), 0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 1.80 (3H, s), 2.13-2.29 (1H, m), 2.40 (3H, s), 2.54 (3H, s), 2.57-2.64 (1H, m), 2.75 (2H, d, J = 7.4 Hz), 3.23 (2H, s), 4.05 (2H, s), 4.20 (1H, brs), 6.94 (2H, d, J = 7.9 Hz), 7.23 (2H, d, J = 7.9 Hz).

2) 2-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N-cyclopropylacetamide dihydrochloride (100 mg, yield 89%) was obtained as a white powder from tert-butyl {[5-[2-(cyclopropylamino)-2-oxoethyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (120 mg, 0.258 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR ($DMSO-d_6$) :0.34 (2H, s), 0.57 (2H, d, J = 5.5 Hz), 0.99

(6H, d, J = 6.2 Hz), 2.11-2.25 (1H, m), 2.41 (3H, s), 2.53-2.58 (1H, m), 2.81 (2H, s), 3.24 (2H, s), 3.6-3.9 (5H, m), 7.20 (2H, d, J = 7.7 Hz), 7.37 (2H, d, J = 7.7 Hz), 8.08 (1H, d, J = 3.4 Hz), 8.56 (3H, brs).

Example 312

{[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(2-morpholin-4-yl-2-oxoethyl)pyridin-3-yl]methyl}amine dihydrochloride

1) tert-Butyl {[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(2-morpholin-4-yl-2-oxoethyl)pyridin-3-yl]methyl}carbamate (50 mg, yield 22%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (200 mg, 0.469 mmol) and morpholine (123 mg, 1.41 mmol) according to a method similar to the method of Example 311-1).

^{1}H-NMR ($CDCl_3$) : 0.97 (6H, d, J = 6.6 Hz), 1.37 (9H, s), 2.09-2.27 (1H, m), 2.41 (3H, s), 2.50 (3H, s), 2.73 (2H, d, J = 7.4 Hz), 3.17 (2H, d, J = 4.1 Hz), 3.30 (2H, s), 3.41 (2H, d, J = 4.1 Hz), 3.56 (4H, dd, J = 16.5, 4.1 Hz), 4.04 (2H, d, J = 4.52 Hz), 4.20 (1H, brs), 6.98 (2H, d, J = 7.9 Hz), 7.22 (2H, d, J = 7.9 Hz).

2) {[2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-(2-morpholin-4-yl-2-oxoethyl)pyridin-3-yl]methyl}amine dihydrochloride (40 mg, yield 94%) was obtained as a white powder from tert-butyl {[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(2-morpholin-4-yl-2-oxoethyl)pyridin-3-yl]methyl}carbamate (45 mg, 0.0908 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.4 Hz), 2.09-2.30 (1H, m), 2.41 (3H, s), 2.50 (3H, s), 2.79 (2H, s), 3.09-3.42 (10H, m), 3.82 (2H, d, J = 3.8 Hz), 7.16 (2H, d, J = 7.7 Hz), 7.39 (2H, d, J = 7.7 Hz), 8.52 (3H, brs).

Example 313

2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N-benzylacetamide dihydrochloride

1) tert-Butyl {[5-[2-(benzylamino)-2-oxoethyl]-2-isobutyl-6-

methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (150 mg, yield 62%) was obtained as a white powder from [5-({[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (200 mg, 0.469 mmol) and benzylamine (151 mg, 1.41 mmol) according to a method similar to the method of Example 311-1).

^{1}H-NMR ($CDCl_3$) : 0.96 (6H, d, J = 6.6 Hz), 1.37 (9H, s), 2.12-2.27 (1H, m), 2.37 (3H, s), 2.56 (3H, s), 2.74 (2H, d, J = 7.2 Hz), 3.32 (2H, s), 4.02 (2H, d, J = 5.1 Hz), 4.20 (1H, brs), 4.34 (2H, d, J = 5.8 Hz), 5.45 (1H, brs), 6.88 (2H, d, J = 7.9 Hz), 7.10-7.20 (4H, m), 7.25-7.35 (3H, m).

2) 2-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N-benzylacetamide dihydrochloride (125 mg, yield 100%) was obtained as a white powder from tert-butyl {[5-[2-(benzylamino)-2-oxoethyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (130 mg, 0.252 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.4 Hz), 2.07-2.28 (1H, m), 2.40 (3H, s), 2.83 (3H, s), 3.28 (2H, d, J = 7.0 Hz), 3.42 (2H s), 3.81 (2H, d, J = 3.0 Hz), 4.21 (2H, d, J = 5.7 Hz), 7.10-7.44 (9H, m), 8.52 (3H, brs).

Example 314

[(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(1H-tetrazol-5-yl)phenoxy]methyl}pyridin-3-yl)methyl]amine dihydrochloride

1) tert-Butyl {[5-[(2-cyanophenoxy)methyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (586 mg, yield 70%) was obtained as a colorless oil from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.67 g, 1.68 mmol) and 2-hydroxybenzonitrile (221 mg, 1.85 mmol) according to a method similar to the meth d of Example 214-1).

^{1}H-NMR ($CDCl_3$) :1.00 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.19-2.28 (1H, m), 2.34 (3H, s), 2.66 (3H, s), 2.79 (2H, d, J = 7.2

Hz), 4.09-4.11 (2H, m), 4.26 (1H, brs), 4.73 (2H, s), 6.76 (1H, d, J = 8.5 Hz), 6.96-7.01 (2H, m), 7.09 (2H, d, J = 8.1 Hz), 7.18 (2H, d, J = 7.9 Hz), 7.40-7.46 (1H, m), 7.50-7.56 (1H, m).

2) tert-Butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(1H-tetrazol-5-yl)phenoxy]methyl}pyridin-3-yl)methyl]carbamate (400 mg, yield 63%) was obtained as a white solid from tert-butyl {[5-[(2-cyanophenoxy)methyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (586 mg, 1.17 mmol) according to a method similar to the method of Example 251-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.17-2.28 (1H, m), 2.32 (3H, s), 2.59 (3H, s), 2.82 (2H, d, J = 7.4 Hz), 4.09-4.13 (2H, m), 4.31 (1H, brs), 4.92 (2H, s), 6.91-6.95 (3H, m), 7.12 (2H, d, J = 7.7 Hz), 7.18 (1H, t, J = 7.6 Hz), 7.43-7.49 (1H, m), 8.42 (2H, dd, J = 7.9, 1.7 Hz).

3) [(2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(1H-tetrazol-5-yl)phenoxy]methyl}pyridin-3-yl)methyl]amine dihydrochloride (327 mg, yield 86%) was obtained as a white solid from tert-butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[2-(1H-tetrazol-5-yl)phenoxy]methyl}pyridin-3-yl)methyl]carbamate (400 mg, 0.737 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.01 (6H, d, J = 6.6 Hz), 2.17-2.29 (4H, m), 2.88 (3H, brs), 3.16 (2H, brs), 3.80 (2H, brs), 4.89 (2H, s), 7.03-7.10 (3H, m), 7.13-7.17 (3H, m), 7.46-7.52 (1H, m), 7.87 (1H, d, J = 7.7 Hz), 8.41 (3H, brs).

Example 315

5-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methylene}-1,3-thiazolidine-2,4-dione dihydrochloride

1) A mixture of tert-butyl {[5-formyl-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (600 mg, 1.51 mmol), 1,3-thiazolidine-2,4-dione (177 mg, 1.51 mmol), piperidine (0.015 mL) and ethanol (10 mL) was stirred with heating at 80 C for 3.5 days. After allowing to cool to room temperature, the

solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl {[5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (400 mg, yield 53%) as a white powder.

^{1}H-NMR ($CDCl_3$) : 0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.12-2.31 (1H, m), 2.38 (3H, s), 2.50 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 4.12 (2H, d, J = 5.1 Hz), 4.20 (1H, brs), 6.96 (2H, d, J = 8.1 Hz), 7.19 (2H, d, J = 8.1 Hz), 7.51 (1H, s).

2) 5-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methylene}-1,3-thiazolidine-2,4-dione dihydrochloride (155 mg, yield 100%) was obtained as a white powder from tert-butyl {[5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (157 mg, 0.316 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.4 Hz), 2.14-2.29 (1H, m), 2.37 (3H, s), 2.51 (3H, s), 3.08 (2H, d, J = 6.4 Hz), 3.83 (2H, d, J = 4.7 Hz), 7.23 (2H, d, J = 8.1 Hz), 7.28-7.40 (3H, m), 8.49 (3H, brs).

Example 316

2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methylbenzoic acid dihydrochloride

1) 2-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methylbenzoic acid (280 mg, yield 93%) was obtained as a white powder from methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methylbenzoate (300 mg, 0.563 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :1.07 (6H, d, J = 6.4 Hz), 1.38 (9H, s), 1.96 (3H, s), 2.24-2.32 (1H, m), 2.36 (3H, s), 3.14 (3H, s), 3.31 (2H, d, J = 6.8 Hz), 4.06 (2H, d, J = 4.3 Hz), 4.20 (1H, brs),

4.83 (2H, s), 6.60 (2H, d, J = 7.5 Hz), 7.02-7.13 (3H, m), 7.19-7.24 (1H, m), 7.45-7.54 (1H, m).

2) 2-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methylbenzoic acid dihydrochloride (55 mg, yield 100%) was obtained as a white powder from 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methylbenzoic acid (58.4 mg, 0.110 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.4 Hz), 1.79 (3H, s), 2.14-2.28 (1H, m), 2.36 (3H, s), 2.97 (3H, s), 3.26 (2H, d, J = 6.8 Hz), 3.77 (2H, d, J = 4.0 Hz), 4.81 (2H, s), 6.93 (2H, d, J = 7.9 Hz), 7.09 (1H, t, J = 7.5 Hz), 7.19 (2H, d, J = 7.9 Hz), 7.29 (1H, d, J = 6.6 Hz), 7.38-7.46 (1H, m), 8.57 (3H, brs).

Example 317

2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-chlorobenzamide dihydrochloride

1) 2-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-chlorobenzoic acid (0.54 g, yield 97%) was obtained as a white powder from methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-chlorobenzoate (0.57 g, 1.0 mmol) according to a method similar to the method of Example 43-1).

^{1}H-NMR ($CDCl_3$) : 1.04 (6H, d, J = 6.6 Hz), 1.37 (9H, s), 2.20-2.35 (1H, m), 2.40 (3H, s), 3.00 (3H, s), 3.21 (2H, d, J = 5.2 Hz), 4.17 (2H, d, J = 5.8 Hz), 4.50-4.65 (1H, m), 4.88 (2H, s), 6.62 (1H, d, J = 8.9 Hz), 7.05 (2H, d, J = 7.8 Hz), 7.25 (2H, d, J = 7.8 Hz), 7.33 (1H, dd, J = 2.6, 8.9 Hz), 7.90 (1H, d, J = 8.9 Hz).

2) tert-Butyl {[5-{[2-(aminocarbonyl)-4-chlorophenoxy]methyl}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.20 g, yield 71%) was obtained as a white

powder from 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-chlorobenzoic acid (0.28 g, 0.51 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) : 0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.15-2.35 (1H, m), 2.36 (3H, s), 2.63 (3H, s), 2.80 (2H, d, J = 7.4 Hz), 4.10 (2H, d, J = 5.1 Hz), 4.15-4.30 (1H, m), 4.77 (2H, s), 5.65 (1H, brs), 6.69 (1H, d, J = 8.9 Hz), 6.99 (2H, d, J = 7.9 Hz), 7.18 (2H, d, J = 7.9 Hz), 7.31 (1H, dd, J = 2.8, 8.9 Hz), 7.48 (1H, brs), 8.18 (1H, d, J = 2.8 Hz).

3) 2-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-chlorobenzamide dihydrochloride (0.16 g, yield 99%) was obtained as a white powder from tert-butyl {[5-{[2-(aminocarbonyl)-4-chlorophenoxy]methyl}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.17 g, 0.31 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.15-2.35 (1H, m), 2.36 (3H, s), 2.84 (3H, brs), 3.08 (2H, brs), 3.82 (2H, d, J = 2.6 Hz), 4.79 (2H, s), 6.83 (1H, d, J = 9.0 Hz), 7.25 (2H, d, J = 7.9 Hz), 7.31 (2H, d, J = 7.9 Hz), 7.41 (1H, dd, J = 2.7, 9.0 Hz), 7.52 (2H, brs), 7.55 (1H, d, J = 2.7 Hz), 8.36 (3H, brs).

Example 318

2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-chlorobenzoic acid dihydrochloride

2-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-chlorobenzoic acid dihydrochloride (0.16 g, yield 85%) was obtained as a white powder from 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-5-chlorobenzoic acid (0.20 g, 0.36 mmol) according to a method similar to the method of Example 276-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.15-2.30 (1H, m),

2.36 (3H, s), 2.83 (3H, brs), 3.05 (2H, brs), 3.75-3.90 (2H, m), 4.77 (2H, brs), 6.92 (1H, d, J = 8.9 Hz), 7.24 (2H, d, J = 7.8 Hz), 7.31 (2H, d, J = 7.8 Hz), 7.47 (1H, dd, J = 2.8, 8.9 Hz), 7.61 (1H, d, J = 2.8 Hz), 8.30 (3H, brs).

Example 319

4'-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]biphenyl-4-carboxylic acid dihydrochloride

1) 4-Bromobenzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.92 g, yield 75%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.82 g, 4.41 mmol) and 4-bromobenzyl bromide (1.10 g, 4.41 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.15-2.26 (1H, m), 2.38 (3H, s), 2.53 (3H, s), 2.77 (2H, d, J = 7.2 Hz), 4.11 (2H, d, J = 4.9 Hz), 4.19 (1H, brs), 4.89 (2H, s), 6.91 (2H, d, J = 8.5 Hz), 6.99 (2H, d, J = 8.1 Hz), 7.09 (2H, d, J = 7.7 Hz), 7.39 (2H, d, J = 8.5 Hz).

2) A solution of 4-bromobenzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.09 g, 1.87 mmol), [4-(methoxycarbonyl)phenyl]boronic acid (675 mg, 3.75 mmol), potassium carbonate (388 mg, 2.81 mmol) and tetrakis(triphenylphosphine)palladium(0) (216 mg, 0.187 mmol) in dioxane (15 mL) and water (2.5 mL) was stirred under an argon atmosphere for 12 hrs. The reaction mixture was diluted with ethyl acetate, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give [4'-(methoxycarbonyl)biphenyl-4-yl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-

methylphenyl)nicotinate (570 mg, yield 48%) as a colorless oil.
^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.17-2.26 (1H, m), 2.29 (3H, s), 2.55 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 3.91 (3H, s), 4.16 (2H, d, J = 4.5 Hz), 4.60 (1H, brs), 4.98 (2H, s), 7.07 (2H, d, J = 8.1 Hz), 7.12-7.16 (4H, m), 7.53 (2H, d, J = 8.3 Hz), 7.64 (2H, d, J = 8.7 Hz), 8.10 (2H, d, J = 8.5 Hz).

3) 4'-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]biphenyl-4-carboxylic acid (380 mg, yield 68%) was obtained as a white solid from [4'-(methoxycarbonyl)biphenyl-4-yl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (570 mg, 0.895 mmol) according to a method similar to the method of Example 9-1).
^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.15-2.26 (1H, m), 2.34 (3H, s), 2.56 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 4.11-4.16 (2H, m), 4.23 (1H, brs), 4.99 (2H, s), 7.05 (2H, d, J = 7.9 Hz), 7.13-7.18 (4H, m), 7.55 (2H, d, J = 8.3 Hz), 7.68 (2H, d, J = 8.5 Hz), 8.18 (2H, d, J = 8.3 Hz).

4) 4'-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]biphenyl-4-carboxylic acid dihydrochloride (255 mg, yield 70%) was obtained as a white solid from 4'-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]biphenyl-4-carboxylic acid (380 mg, 0.610 mmol) according to a method similar to the method of Example 2-3).
^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.15-2.26 (1H, m), 2.33 (3H, s), 2.57 (3H, brs), 2.92 (2H, brs), 3.82 (2H, d, J = 4.3 Hz), 5.04 (2H, s), 7.18 (4H, d, J = 8.3 Hz), 7.24 (2H, d, J = 8.1 Hz), 7.68 (2H, d, J = 8.3 Hz), 7.82 (2H, d, J = 8.5 Hz), 8.04 (2H, d, J = 8.5 Hz), 8.34 (3H, brs).

Example 320

pyridin-4-ylmethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate trihydrochloride

1) Pyridin-4-ylmethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (322 mg, yield 53%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.50 g, 1.21 mmol), 4-(chloromethyl)pyridine hydrochloride (0.20 g, 1.21 mmol) and potassium carbonate (0.42 g, 3.0 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.17-2.27 (1H, m), 2.36 (3H, s), 2.56 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 4.14 (2H, d, J = 4.9 Hz), 4.42 (1H, brs), 4.94 (2H, s), 6.89 (2H, d, J = 5.8 Hz), 7.04 (2H, d, J = 8.1 Hz), 7.12 (2H, d, J = 7.9 Hz), 8.48 (2H, d, J = 5.3 Hz).

2) Pyridin-4-ylmethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate trihydrochloride (260 mg, yield 79%) was obtained as a white solid from pyridin-4-ylmethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (322 mg, 0.639 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 2.19-2.27 (1H, m), 2.33 (3H, s), 2.57 (3H, brs), 2.89 (2H, brs), 3.81 (2H, d, J = 5.5 Hz), 5.29 (2H, s), 7.17-7.24 (4H, m), 7.60 (2H, brs), 8.35 (3H, brs), 8.83-8.84 (2H, brs).

Example 321

pyridin-3-ylmethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate trihydrochloride

1) Pyridin-3-ylmethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (454 mg, yield 74%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.50 g, 1.21 mmol), 3-(bromomethyl)pyridine hydrobromide (0.46 g, 1.81 mmol) and

potassium carbonate (0.50 g, 3.6 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.15-2.24 (1H, m), 2.36 (3H, s), 2.54 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 4.12 (2H, d, J = 4.1 Hz), 4.20 (1H, brs), 4.94 (2H, s), 6.99 (2H, d, J = 8.1 Hz), 7.09 (2H, d, J = 7.9 Hz), 7.17-7.21 (1H, m), 7.32-7.37 (1H, m), 8.34 (1H, d, J = 1.7 Hz), 8.55 (1H, dd, J = 4.8, 1.6 Hz).

2) Pyridin-3-ylmethyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate trihydrochloride (183 mg, yield 39%) was obtained as a white solid from pyridin-3-ylmethyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (454 mg, 0.903 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) . :0.96 (6H, d, J = 6.8 Hz), 2.17-2.26 (1H, m), 2.31 (3H, s), 2.59 (3H, s), 2.93 (2H, d, J = 6.0 Hz), 3.78 (2H, d, J = 5.5 Hz), 5.22 (2H, s), 7.12 (4H, s), 7.95 (1H, t, J = 6.7 Hz), 8.14 (1H, d, J = 7.9 Hz), 8.41 (3H, brs), 8.67 (1H, s), 8.90 (1H, d, J = 5.5 Hz).

Example 322

methyl 2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methoxybenzoate dihydrochloride

1) Methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methoxybenzoate (0.62 g, yield 55%) was obtained as a white powder from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.80 g, 2.0 mmol) and methyl 3-methoxysalicylate (0.55 g, 3.0 mmol) according to a method similar to the method of Example 106-1).

^{1}H-NMR ($CDCl_3$) : 0.98 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.15-2.30 (1H, m), 2.34 (3H, s), 2.73 (3H, s), 2.75 (2H, d, J = 7.4 Hz), 3.54 (3H, s), 3.64 (3H, s), 3.97 (2H, d, J = 5.1 Hz), 4.20-4.30 (1H, m), 4.86 (2H, s), 6.60 (2H, d, J = 8.1 Hz), 6.85

(1H, dd, J = 1.5, 8.1 Hz), 7.01 (2H, d, J = 8.1 Hz), 7.06 (1H, d, J = 8.1 Hz), 7.14 (1H, dd, J = 1.5, 8.1 Hz).

2) Methyl 2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methoxybenzoate dihydrochloride (0.12 g, yield 66%) was obtained as a white powder from methyl 2-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methoxybenzoate (0.19 g, 0.34 mmol) according to a method similar to the method of Example 274-2).

^{1}H-NMR (DMSO-d_6) : 0.99 (6H, d, J = 6.6 Hz), 2.10-2.30 (1H, m), 2.37 (3H, s), 2.94 (3H, brs), 3.00-3.20 (2H, m), 3.51 (3H, s), 3.63 (3H, s), 3.72 (2H, brs), 4.88 (2H, brs), 6.77 (2H, d, J = 7.9 Hz), 7.00-7.22 (3H, m), 7.17 (2H, d, J = 7.9 Hz), 8.27 (3H, brs).

Example 323

methyl 2-({[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl}thio)benzoate dihydrochloride

1) Methyl 2-({[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl}thio)benzoate (1.46 g, yield 63%) was obtained as a powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl methanesulfonate (2.0 g, 4.7 mmol) and methyl thiosalicylate (757 mg, 45 mmol) according to a method similar to the method of Example 33-1).

^{1}H-NMR ($CDCl_3$) :1.02 (9H, s), 1.37 (9H, s), 2.34 (3H, s), 2.65 (3H, s), 2.83 (2H, s), 3.89 (3H, s), 4.07 (2H, d, J=4.9 Hz), 4.17 (1H, brs), 7.04-7.18 (6H, m), 7.32-7.38 (1H, m), 7.91-7.95 (1H, m).

2) Methyl 2-({[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl}thio)benzoate dihydrochloride (254 mg, yield 89%) was obtained as a powder from methyl 2-({[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl}thio)benzoate (300 mg, 0.533 mmol) according to a method similar to the method of

Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.03 (9H, s), 2.34 (3H, s), 2.83 (3H, s), 3.18 (2H, brs), 3.80 (3H, s), 3.88 (2H, s), 4.00 (2H, s), 7.23-7.32 (6H, m), 7.47-7.52 (1H, m), 7.85-7.88 (1H, m), 8.21 (3H, brs).

Example 324

2-({[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl}thio)benzoic acid dihydrochloride

1) 4-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl}thio)benzoic acid (897 mg, yield 92%) was obtained as a white solid from methyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl}thio)benzoate (1.0 g, 1.78 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :1.12 (9H, s), 1.38 (9H, s), 2.38 (3H, s), 3.09 (3H, s), 3.47 (2H, s), 3.79 (2H, s), 4.14 (2H, d, J=4.3 Hz), 4.52 (1H, brs), 6.85-6.92 (2H, m), 7.08-7.13 (1H, m), 7.19-7.21 (2H, m), 7.29-7.33 (1H, m), 7.37-7.41 (1H, m), 7.94-7.97 (1H, m).

2) 2-({[5-(Aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl}thio)benzoic acid dihydrochloride (158 mg, yield 83%) was obtained as a white powder from 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl}thio)benzoic acid (200 mg, 0.364 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.03 (9H, s), 2.34 (3H, s), 2.81 (3H, s), 3.15 (2H, brs), 3.80 (2H, s), 3.85 (2H, s), 7.19-7.33 (6H, m), 7.44-7.49 (1H, m), 7.86-7.89 (1H, m), 8.17 (3H, brs).

Example 325

2-({[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl}thio)benzamide dihydrochloride

1) 4-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-2-methyl-4-(4-

methylphenyl)-6-neopentylpyridin-3-yl]methyl}thio)benzamide (349 mg, yield 70%) was obtained as a white solid from 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl}thio)benzoic acid (500 mg, 0.911 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :1.02 (9H, s), 1.37 (9H, s), 2.39 (3H, s), 2.63 (3H, s), 2.83 (2H, s), 3.81 (2H, s), 4.04 (2H, d, J=5.1 Hz), 4.24 (1H, brs), 5.45 (1H, brs), 6.68 (1H, brs), 6.96-6.99 (2H, m), 7.18-7.22 (3H, m), 7.28-7.32 (2H, m), 7.75-7.78 (1H, m).

2) 2-({[5-(Aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl}thio)benzamide dihydrochloride (160 mg, yield 84%) was obtained as a white powder from 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl}thio)benzamide (200 mg, 0.365 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.03 (9H, s), 2.37 (3H, s), 2.76 (3H, s), 3.17 (2H, brs), 3.75-3.85 (4H, m), 7.14-7.35 (7H, m), 7.40 (1H, s), 7.50-7.48 (1H, m), 7.81 (1H, s), 8.20 (3H, brs).

Example 326

2-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methylbenzamide dihydrochloride

1) tert-Butyl ([5-{[2-(aminocarbonyl)-6-methylphenoxy]methyl}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (190 mg, yield 95%) was obtained as a white powder from 2-{[5-({[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methylbenzoic acid (200 mg, 0.375 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :1.05 (6H, d, J = 6.2 Hz), 1.40 (9H, s), 1.93 (3H, s), 2.21-2.32 (1H, m), 2.36 (3H, s), 3.01 (3H, s), 3.16 (2H, d, J = 6.8 Hz), 4.04 (2H, s), 4.20 (1H, brs), 4.81 (2H,

s),5.80 (1H, brs), 6.40 (1H, brs), 6.65 (2H, s), 7.02-7.23 (4H, m), 7.56 (1H, s).

2) 2-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-3-methylbenzamide dihydrochloride (100 mg, yield 70%) was obtained as a white powder from tert-butyl {[5-{[2-(aminocarbonyl)-6-methylphenoxy]methyl}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (150 mg, 0.282 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.4 Hz), 1.76 (3H, s), 2.13-2.29 (1H, m), 2.37 (3H, s), 2.96 (3H, s), 3.21 (2H, d, J = 6.6 Hz), 3.76 (2H, d, J = 4.9 Hz), 4.78 (2H, s), 7.01 (2H, d, J = 7.9 Hz), 7.04-7.08 (1H, m), 7.15-7.26 (4H, m), 7.34 (1H, brs), 7.53 (1H, brs), 8.52 (3H, brs).

Example 327

2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N-phenylacetamide dihydrochloride

1) tert-Butyl {[5-(2-anilino-2-oxoethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (220 mg, yield 94 %) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (200 mg, 0.469 mmol) and aniline (150 mg, 1.41 mmol) according to a method similar to the method of Example 311-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.15-2.29 (1H, m), 2.40 (3H, s), 2.63 (3H, s), 2.77 (2H, d, J = 7.2 Hz), 3.66 (3H, s), 4.06 (2H, d, J = 4.9Hz), 4.20 (1H, brs), 7.02 (2H, d, J = 7.9 Hz), 7.06-7.14 (1H, m), 7.24 (2H, d, J = 7.9 Hz), 7.27-7.39 (4H, m).

2) 2-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N-phenylacetamide dihydrochloride (200 mg, yield 100%) was obtained as a white powder from tert-butyl {[5-(2-anilino-2-oxoethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (210 mg, 0.419 mmol)

according to a method similar to the method of Example 2-3).
^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 5.5 Hz), 2.13-2.28 (1H, m), 2.38 (3H, s), 2.85 (3H, s), 3.25 (2H, s), 3.62 (2H, s), 3.83 (2H, s), 7.04 (1H, t, J = 6.7 Hz), 7.15-7.42 (6H, m), 7.50 (2H, d, J = 7.4 Hz), 8.53 (3H, brs), 10.20 (1H, s).

Example 328

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]cyclohexanecarboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]cyclohexanecarboxamide dihydrochloride (230 mg, yield 98%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and cyclohexanecarbonyl chloride (100 L, 0.75 mmol) according to a method similar to the method of Example 223.
^{1}H-NMR (DMSO-d_6) : 0.98 (6H, d, J = 6.6 Hz), 1.00-1.25 (6H, m), 1.41 (2H, brs), 1.59 (2H, brs), 2.08-2.22 (2H, m), 2.37 (3H, s), 2.53 (3H, s), 3.03 (2H, brs), 3.81 (2H, s), 7.14 (2H, d, J = 7.8 Hz), 7.30 (2H, d, J = 7.8 Hz), 8.33 (3H, brs), 9.37 (1H, brs).

Example 329

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]piperidine-1-carboxamide dihydrochloride

1) tert-Butyl ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(piperidin-1-ylcarbonyl)amino]pyridin-3-yl}methyl)carbamate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and piperidine (150 L, 1.5 mmol) according to a method similar to the method of Example 95-1).
EIMS(M+1):495

2) N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-

methylphenyl)pyridin-3-yl]piperidine-1-carboxamide dihydrochloride (218 mg, yield 47%) was obtained as a white powder from the oil obtained in aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.3 Hz), 1.07-1.19 (4H, m), 1.44 (2H, brs), 2.12-2.27 (1H, m), 2.37 (3H, s), 2.60 (3H, s), 3.05 (2H, brs), 3.15 (4H, brs), 3.83 (2H, s), 7.19 (2H, d, J = 7.8 Hz), 7.31 (2H, d, J = 7.8 Hz), 7.96 (1H, brs), 8.27 (3H, brs).

Example 330

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]tetrahydro-2H-pyran-4-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]tetrahydro-2H-pyran-4-carboxamide dihydrochloride (232 mg, yield 98%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and tetrahydro-2H-pyran-4-carbonyl chloride (111 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 0.98 (6H, d, J = 6.6 Hz), 1.00-1.25 (6H, m), 1.41 (2H, brs), 1.59 (2H, brs), 2.08-2.22 (2H, m), 2.37 (3H, s), 2.53 (3H, s), 3.03 (2H, brs), 3.81 (2H, s), 7.14 (2H, d, J = 7.5 Hz), 7.30 (2H, d, J = 7.8 Hz), 8.27 (3H, brs), 9.43 (1H, brs).

Example 331

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]morpholine-4-carboxamide dihydrochloride

1) tert-Butyl ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(morpholin-4-ylcarbonyl)amino]pyridin-3-yl}methyl)carbamate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and morpholine

(130 L, 1.5 mmol) according to a method similar to the method of Example 95-1).

EIMS(M+1):497

2) N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]morpholine-4-carboxamide dihydrochloride (278 mg, yield 59%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.3 Hz), 2.10-2.27 (1H, m), 2.39 (3H, s), 2.70 (3H, s), 3.14 (6H, brs), 3.19 (4H, brs), 3.86 (2H, brs), 7.21 (2H, d, J = 7.8 Hz), 7.34 (2H, d, J = 7.8 Hz), 8.44 (4H, brs).

Example 332

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]piperidine-4-carboxamide trihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]piperidine-4-carboxamide trihydrochloride (246 mg, yield 98%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and benzyl 4-(chlorocarbonyl)piperidine-1-carboxylate (210 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 0.98 (6H, d, J = 6.6 Hz), 1.44 (4H, brs), 2.15-2.26 (1H, m), 2.38 (3H, s), 2.38-2.57 (1H, m), 2.57 (3H, s), 2.76 (2H, brs), 3.07 (4H, brs), 3.81 (2H, brs), 7.17 (2H, d, J = 8.1 Hz), 7.30 (2H, d, J = 8.1 Hz), 8.41 (3H, brs), 8.80 (1H, brs), 9.09 (1H, brs), 9.84 (1H, brs).

Example 333

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]piperazine-1-carboxamide trihydrochloride

1) tert-Butyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-

isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)piperazine-1-carboxylate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and tert-butyl piperazine-1-carboxylate (140 mg, 1.5 mmol) according to a method similar to the method of Example 95-1).
EIMS(M+1):596

2) N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]piperazine-1-carboxamide trihydrochloride (250 mg, yield 97%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).
^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.3 Hz), 2.15-2.26 (1H, m), 2.42 (3H, s), 2.62 (2H, s), 2.72 (3H, s), 3.05 (2H, brs), 3.42 (4H, brs), 3.82 (2H, brs), 7.19 (2H, d, J = 7.5 Hz), 7.31 (2H, d, J = 7.5 Hz), 8.37 (3H, brs), 8.60 (1H, brs), 9.41 (2H, brs).

Example 334

(5-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid dihydrochloride

1) (5-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid (355 mg, yield 50%) was obtained as a yellow powder from tert-butyl ([5-formyl-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (500 mg, 1.26 mmol) and (4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid (241 mg, 1.26 mmol) according to a method similar to the method of Example 315-1).
^{1}H-NMR ($CDCl_3$) : 0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.09-2.27 (1H, m), 2.36 (3H, s), 2.50 (3H, s), 2.8 (2H, d, J = 7.4 Hz), 4.01-4.18 (4H, m), 4.20 (1H, brs), 6.96 (2H, d, J = 7.9 Hz), 7.20 (2H, d, J = 7.9 Hz), 7.38 (1H, s).

2) (5-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methylene}-4-oxo-2-thioxo-1,3-

thiazolidin-3-yl)acetic acid dihydrochloride (198 mg, yield 100%) was obtained as a yellow powder from (5-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid (210 mg, 0.386 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.4 Hz), 2.17-2.31 (1H, m), 2.36 (3H, s), 2.55 (3H, s), 2.95 (2H, d, J = 6.6 Hz), 3.80 (2H, d, J = 7.4 Hz), 4.63 (2H, s), 7.22 (2H, d, J = 8.1 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.55 (1H, s), 8.35 (3H, brs).

Example 335

5-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methylene}-2-thioxo-1,3-thiazolidin-4-one dihydrochloride

1) tert-Butyl ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-oxo-2-thioxo-1,3-thiazolidine-5-ylidene)methyl]pyridin-3-yl}methyl)carbamate (310 mg, yield 48%) was obtained as a yellow powder from tert-butyl ([5-formyl-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl)carbamate (500 mg, 1.26 mmol) and 2-thioxo-1,3-thiazolidin-4-one (168 mg, 1.26 mmol) according to a method similar to the method of Example 315-1).

^{1}H-NMR ($CDCl_3$) : 0.98 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.15-2.31 (1H, m), 2.37 (3H, s), 2.50 (3H, s), 2.80 (2H, d, J = 7.4 Hz), 4.13 (2H, d, J = 7.4 Hz), 4.20 (1H, brs), 6.95 (2H, d, J = 7.7 Hz), 7.20 (2H, d, J = 7.7 Hz), 7.34 (1H, s).

2) 5-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methylene}-2-thioxo-1,3-thiazolidin-4-one dihydrochloride (173 mg, yield 100%) was obtained as a yellow powder from tert-butyl ({2-isobutyl-6-methyl-4-(4-methylphenyl)-5-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]pyridin-3-yl}methyl)carbamate (200 mg, 0.390 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 2.11-2.31 (1H, m),

2.36 (3H, s), 2.52 (2H, s), 2.90 (3H, s), 3.79 (2H, s), 7.19 (2H, d, J = 8.1 Hz), 7.26-7.37 (3H, m), 8.27 (3H, brs).

Example 336

methyl 3-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoate dihydrochloride

1) Methyl 3-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoate (230 mg, yield 35 %) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (500 mg, 1.17 mmol) and methyl 3-aminobenzoate (532 mg, 3.52 mmol) according to a method similar to the method of Example 311-1).

^{1}H-NMR ($CDCl_3$) : 0.98 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.16-2.31 (1H, m), 2.41 (3H, s), 2.64 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.47 (2H, s), 3.91 (3H, s), 4.07 (2H, d, J = 4.5 Hz), 4.20 (1H, brs), 5.50 (1H, brs), 7.02 (2H, d, J = 7.9 Hz), 7.24 (2H, d, J = 7.9 Hz), 7.38 (1H, t, J = 7.9 Hz), 7.72-7.86 (3H, m).

2) Methyl 3-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoate dihydrochloride (65 mg, yield 91%) was obtained as a white powder from methyl 3-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoate (75.2 mg, 0.134 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.11-2.30 (1H, m), 2.36 (3H, s), 2.53 (3H, s), 2.68 (2H, s), 2.98 (2H, s), 3.78 (2H, s), 3.84 (3H, s), 7.19 (2H, d, J = 8.1 Hz), 7.32 (2H, d, J = 8.1 Hz), 7.44 (1H, t, J = 7.9 Hz), 7.61-7.71 (2H, m), 8.10 (3H, brs), 8.20 (1H, s), 10.6 (1H, brs).

Example 337

methyl 3-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)pyridine-2-carboxylate trihydrochloride

1) Methyl 3-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)pyridine-2-carboxylate (1.43 g, 2.60 mmol) was obtained as a yellow oil from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (2.08 g, 5.22 mmol) and methyl 3-mercaptopyridine-2-carboxylate (883 mg, 5.22 mmol) according to a method similar to the method of Example 183-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.14-2.26 (1H, m), 2.35 (3H, s), 2.66 (3H, s), 2.76 (2H, d, J = 7.2 Hz), 3.76 (2H, s), 3.99 (3H, s), 4.03 (2H, d, J = 5.3 Hz), 4.19 (1H, brs), 7.04-7.07 (1H, m), 7.09 (2H, d, J = 8.1 Hz), 7.18 (2H, d, J = 7.7 Hz), 7.28-7.31 (1H, m), 7.40-7.44 (1H, m), 8.43 (1H, dd, J = 4.5, 1.5 Hz).

2) Methyl 3-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)pyridine-2-carboxylate trihydrochloride (161 mg, yield 80%) was obtained as a pale-yellow solid from methyl 3-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)pyridine-2-carboxylate (197 mg, 0.359 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.4 Hz), 2.15-2.26 (1H, m), 2.35 (3H, s), 2.89 (3H, brs), 3.18 (2H, brs), 3.77 (2H, d, J = 5.1 Hz), 3.83 (3H, s), 3.94 (2H, s), 7.25 (2H, d, J = 7.9 Hz), 7.31 (2H, d, J = 8.1 Hz), 7.51 (1H, dd, J = 8.3, 4,5 Hz), 7.76 (1H, d, J = 8.1 Hz), 8.35-8.53 (4H, m).

Example 338

3-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)pyridine-2-carboxylic acid trihydrochloride

1) 3-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)pyridine-2-carboxylic acid (1.19 g, yield 99%) was obtained as a colorless

oil from methyl 3-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)pyridine-2-carboxylate (1.23 g, 2.24 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :1.06 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.21-2.32 (1H, m), 2.37 (3H, s), 2.97 (3H, brs), 3.17 (2H, brs), 3.81 (2H, s), 4.08-4.13 (2H, m), 4.31 (1H, brs), 7.14 (2H, d, J = 7.9 Hz), 7.24 (2H, d, J = 8.3 Hz), 7.42-7.46 (1H, m), 7.50-7.53 (1H, m), 8.35 (1H, dd, J = 4.4, 1.2 Hz).

2) 3-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)pyridine-2-carboxylic acid trihydrochloride (265 mg, yield 69%) was obtained as a pale-yellow solid from 3-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)pyridine-2-carboxylic acid (0.38 g, 0.709 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.13-2.24 (1H, m), 2.34 (3H, s), 2.79-2.82 (3H, m), 3.05 (2H, brs), 3.75 (2H, brs), 3.89 (2H, brs), 7.26 (2H, d, J = 6.4 Hz), 7.31 (2H, d, J = 8.3 Hz), 7.48 (1H, dd, J = 8.3, 4.5 Hz), 7.72 (1H, d, J = 8.3 Hz), 8.19-8.36 (3H, m), 8.43 (1H, d, J = 4.5 Hz).

Example 339

3-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)pyridine-2-carboxamide trihydrochloride

1) tert-Butyl {[5-({[2-(aminocarbonyl)pyridin-3-yl]thio}methyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (720 mg, yield 88%) was obtained as a colorless oil from 3-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)pyridine-2-carboxylic acid (0.82 g, 1.53 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.14-

2.26 (1H, m), 2.33 (3H, s), 2.67 (3H, s), 2.75 (2H, d, J = 7.2 Hz), 3.71 (2H, s), 4.03 (2H, d, J = 4.9 Hz), 4.18 (1H, brs), 5.44 (1H, brs), 7.12-7.18 (4H, m), 7.25-7.29 (1H, m), 7.42 (1H, dd, J = 8.3, 1.3 Hz), 7.82 (1H, brs), 8.24 (1H, dd, J = 4.3, 1.3 Hz).

2) 3-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}thio)pyridine-2-carboxamide trihydrochloride (546 mg, yield 74%) was obtained as a pale-yellow solid from tert-butyl {[5-({[2-(aminocarbonyl)pyridin-3-yl]thio}methyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (720 mg, 1.35 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.01 (6H, d, J = 6.6 Hz), 2.13-2.26 (1H, m), 2.34 (3H, s), 2.96 (3H, s), 3.25 (2H, brs), 3.79 (2H, d, J = 5.1 Hz), 3.86 (2H, s), 7.29-7.40 (4H, m), 7.46 (1H, dd, J = 8.1, 4.5 Hz), 7.64 (1H, brs), 7.69 (1H, d, J = 7.5 Hz), 8.09 (1H, brs), 8.36 (1H, dd, J = 4.5, 1.2 Hz), 8.51 (3H, brs).

Example 340

4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]cyclohexanecarboxylic acid dihydrochloride

1) A mixture of methyl 4-(hydroxymethyl)cyclohexanecarboxylate (0.40 g, 2.32 mmol), triethylamine (0.65 mL, 4.64 mmol) and tetrahydrofuran (10 mL) was cooled to 0 C and methanesulfonyl chloride (0.27 mL, 3.48 mmol) was added dropwise. After stirring at room temperature for 30 min., the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to give methyl 4-{[(methylsulfonyl)oxy]methyl}cyclohexanecarboxylate as a crude product. The crude product was dissolved in N,N-dimethylformamide (15 mL), and potassium carbonate (480 mg,

3.48 mmol) and 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.95 g, 2.32 mmol) were added. The mixture was stirred with heating at 70 C for 1 hr. The reaction mixture was diluted with ethyl acetate, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give [4-(methoxycarbonyl)cyclohexyl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (750 mg, yield 57%) as a colorless oil.
^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.07-1.18 (2H, m), 1.33-1.49 (14H, m), 1.83-1.96 (2H, m), 2.16-2.25 (1H, m), 2.39 (3H, s), 2.48-2.56 (4H, m), 2.78 (2H, d, J = 7.4 Hz), 3.67 (3H, s), 3.78 (2H, d, J = 6.8 Hz), 4.13-4.17 (2H, m), 4.23 (1H, brs), 7.07 (2H, d, J = 7.9 Hz), 7.20 (2H, d, J = 7.7 Hz).

2) 4-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]cyclohexanecarboxylic acid (550 mg, yield 75%) was obtained as a white solid from [4-(methoxycarbonyl)cyclohexyl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (750 mg, 1.32 mmol) according to a method similar to the method of Example 9-1).
^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.08-1.20 (2H, m), 1.33-1.68 (14H, m), 1.86-1.96 (2H, m), 2.15-2.28 (1H, m), 2.38 (3H, s), 2.54-2.60 (4H, m), 2.78 (2H, brs), 3.78 (2H, d, J = 6.6 Hz), 4.12-4.16 (2H, m), 4.24 (1H, brs), 7.07 (2H, d, J = 7.9 Hz), 7.20 (2H, d, J = 7.7 Hz).

3) 4-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]cyclohexanecarboxylic acid dihydrochloride (254 mg, yield 83%) was obtained as a white solid from 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-

isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]cyclohexanecarboxylic acid (320 mg, 0.579 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 1.17-1.42 (7H, m), 1.66-1.82 (2H, m), 2.14-2.24 (1H, m), 2.37 (3H, s), 2.41-2.45 (1H, m), 2.54 (3H, s), 2.86-2.97 (2H, m), 3.76 (2H, d, J = 6.6 Hz), 3.83 (2H, d, J = 4.7 Hz), 7.20 (2H, d, J = 7.9 Hz), 7.30 (2H, d, J = 8.1 Hz), 8.34 (3H, brs).

Example 341

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]thiophene-2-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]thiophene-2-carboxamide dihydrochloride (171mg, yield 75%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and thiophene-2-carbonyl chloride (110 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 1.00 (6H, d, J = 6.6 Hz), 2.20-2.31 (1H, m), 2.31 (3H, s), 2.63 (3H, s), 3.07 (2H, brs), 3.86 (2H, s), 7.12 (1H, dd, J = 3.3, 4.8 Hz), 7.25 (4H, s), 7.74 (1H, d, J = 3.3 Hz), 7.79 (1H, d, J = 4.8 Hz), 8.42 (3H, brs), 10.18 (1H, brs).

Example 342

3-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoic acid dihydrochloride

1) 3-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoic acid (110 mg, yield 87%) was obtained as a white powder from methyl 3-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoate

(130 mg, 0.232 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) : 0.94 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.10-2.27 (1H, m), 2.36 (3H, s), 2.89-3.10 (5H, m), 3.90 (2H, d, J = 5.7 Hz), 4.10 (2H, d, J = 7.2 Hz), 4.20 (1H, brs), 4.90 (1H, brs), 7.13 (2H, d, J = 8.1 Hz), 7.24 (2H, d, J = 8.1 Hz), 7.32 (1H, t, J = 8.0 Hz), 7.65 (1H, d J = 7.7 Hz), 7.89 (1H, s), 8.17 (1H, s).

2) 3-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoic acid dihydrochloride (95 mg, yield 95%) was obtained as a white powder from 3-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoic acid (105 mg, 0.192 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.8 Hz), 2.08-2.25 (1H, m), 2.37 (3H, s), 2.51 (3H, s), 2.83 (2H, s), 3.20 (2H, s), 3.82 (2H, s), 7.09-7.51 (5H, m), 7.54-7.79 (2H, m), 8.14 (1H, s), 8.44 (3H, s), 10.34 (1H, brs).

Example 343

methyl 4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]benzoate dihydrochloride

1) Methyl 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]benzoate (350 mg, yield 67%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (390 mg, 0.914 mmol) and methyl 4-(aminomethyl)benzoate (553 mg, 2.74 mmol) according to a method similar to the method of Example 311-1).

^{1}H-NMR ($CDCl_3$) : 0.96 (6H, d, J = 6.6 Hz), 1.37 (9H, s), 2.11-2.29 (1H, m), 2.39 (3H, s), 2.55 (3H, s), 2.74 (2H, d, J = 7.2 Hz), 3.35 (2H, s), 3.93 (3H, s), 4.02 (2H, d, J = 5.1 Hz), 4.20

(1H, brs), 4.39 (2H, d, J = 5.8 Hz), 5.49 (1H, brs), 6.90 (2H, d, J = 7.9 Hz), 7.16 (2H, d, J = 7.9 Hz), 7.23 (2H, d, J = 8.1 Hz), 7.99 (2H, d, J = 8.1 Hz).

2) Methyl 4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]benzoate dihydrochloride (51 mg, yield 89%) was obtained as a white powder from methyl 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]benzoate (60 mg, 0.105 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.11-2.27 (1H, m), 2.40 (3H, s), 2.81 (3H, s), 3.24 (2H, d, J = 6.0 Hz), 3.44 (2H, s), 3.78-3.89 (5H, m), 4.28 (2H, d, J = 5.5 Hz), 7.20 (2H, d, J = 7.9 Hz), 7.27-7.38 (5H, m), 7.94 (2H, d, J = 7.9 Hz), 8.54 (3H, brs).

Example 344

5-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]pyrazine-2-carboxylic acid dihydrochloride

1) Methyl 5-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]pyrazine-2-carboxylate (1.35 g, yield 98%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.00 g, 2.43 mmol) and methyl 5-(bromomethyl)pyrazine-2-carboxylate (0.51 g, 2.21 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.17-2.27 (1H, m), 2.31 (3H, s), 2.58 (3H, s), 2.79 (2H, d, J = 7.2 Hz), 4.06 (3H, s), 4.12-4.16 (2H, m), 4.22 (1H, brs), 5.13 (2H, s), 7.02 (2H, d, J = 8.1 Hz), 7.10 (2H, d, J = 7.9 Hz), 8.36 (1H, d, J = 1.3 Hz), 9.19 (1H, d, J = 1.3 Hz).

2) 5-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-

methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]pyrazine-2-carboxylic acid (600 mg, yield 45%) was obtained as a colorless oil from methyl 5-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]pyrazine-2-carboxylate (1.35 g, 2.40 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.16-2.28 (1H, m), 2.33 (3H, s), 2.59 (3H, s), 2.82 (2H, d, J = 7.4 Hz), 4.11-4.19 (2H, m), 4.24 (1H, brs), 5.18 (2H, s), 7.04 (2H, d, J = 7.9 Hz), 7.12 (2H, d, J = 7.2 Hz), 8.20 (1H, s), 9.30 (1H, s).

3) 5-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]pyrazine-2-carboxylic acid dihydrochloride (497 mg, yield 76%) was obtained as a yellow solid from 5-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]pyrazine-2-carboxylic acid (600 mg, 1.09 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 2.17-2.26 (1H, m), 2.29 (3H, s), 2.62 (3H, brs), 2.94 (2H, brs), 3.80 (2H, d, J = 4.7 Hz), 5.23 (2H, s), 7.08-7.18 (4H, m), 8.38 (3H, brs), 8.43 (1H, d, J = 1.3 Hz), 9.10 (1H, d, J = 1.3 Hz).

Example 345

4-bromobenzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

4-Bromobenzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (628 mg, yield 90%) was obtained as a white solid from 4-bromobenzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.73 g, 1.26 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.8 Hz), 2.14-2.27 (1H, m),

2.36 (3H, s), 2.87 (2H, brs), 3.80 (2H, d, J = 5.3 Hz), 4.97 (2H, s), 7.00 (2H, d, J = 8.5 Hz), 7.12 (2H, d, J = 8.1 Hz), 7.19 (2H, d, J = 8.1 Hz), 7.50 (2H, d, J = 8.5 Hz), 8.26 (3H, brs).

Example 346

{[5-[(2-bromophenoxy)methyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amine dihydrochloride

1) tert-Butyl {[5-[(2-bromophenoxy)methyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (640 mg, yield 46%) was obtained as a white solid from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.00 g, 2.51 mmol) and 2-bromophenol (478 mg, 2.76 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.19-2.28 (1H, m), 2.37 (3H, s), 2.69 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 4.08-4.11 (2H, m), 4.24 (1H, brs), 4.67 (2H, s), 6.65 (1H, dd, J = 8.1, 1.3 Hz), 6.79-6.84 (1H, m), 7.07 (2H, d, J = 8.1 Hz), 7.12-7.19 (3H, m), 7.51 (1H, dd, J = 7.9, 1.5 Hz).

2) {[5-[(2-Bromophenoxy)methyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}amine dihydrochloride (458 mg, yield 75%) was obtained as a white solid from tert-butyl {[5-[(2-bromophenoxy)methyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (640 mg, 1.16 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.01 (6H, d, J = 6.6 Hz), 2.16-2.30 (1H, m), 2.36 (3H, s), 2.91 (3H, brs), 3.20 (2H, brs), 3.79-3.90 (2H, m), 4.79 (2H, s), 6.89-6.95 (2H, m), 7.25-7.36 (5H, m), 7.58 (1H, dd, J = 7.7, 1.5 Hz), 8.48 (3H, brs).

Example 347

4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-methoxybenzoic acid dihydrochloride

1) 2-Methoxy-4-(methoxycarbonyl)benzyl 5-{[(tert-

butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.15 g, yield 100%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.80 g, 1.94 mmol) and methyl 4-(bromomethyl)-3-methoxybenzoate (503 mg, 1.94 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.15-2.24 (1H, m), 2.34 (3H, s), 2.54 (3H, s), 2.77 (2H, d, J = 7.2 Hz), 3.85 (3H, s), 3.93 (3H, s), 4.10-4.16 (2H, m), 4.20 (1H, brs), 5.06 (2H, s), 6.96 (1H, d, J = 7.9 Hz), 7.03 (2H, d, J = 8.1 Hz), 7.10 (2H, d, J = 7.9 Hz), 7.48-7.53 (2H, m).

2) 4-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-methoxybenzoic acid (1.10 g, yield 97%) was obtained as a colorless oil from 2-methoxy-4-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.15 g, 1.94 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.16-2.26 (1H, m), 2.35 (3H, s), 2.56 (3H, s), 2.80 (2H, d, J = 7.2 Hz), 3.86 (3H, s), 4.11-4.16 (2H, m), 4.23 (1H, brs), 5.08 (2H, s), 6.97 (1H, d, J = 7.9 Hz), 7.04 (2H, d, J = 7.7 Hz), 7.11 (2H, d, J = 7.7 Hz), 7.53 (1H, s), 7.58 (1H, d, J = 7.9 Hz).

3) 4-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-methoxybenzoic acid dihydrochloride (247 mg, yield 74%) was obtained as a white solid from 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-methoxybenzoic acid (0.35 g, 0.607 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6Hz), 2.17-2.26 (1H, m), 2.32 (3H, s), 2.84 (2H, brs), 3.79 (2H, d, J = 5.7Hz), 3.83

(3H, s), 5.03 (2H, s), 6.96 (1H, d, J = 7.7Hz), 7.13 (2H, d, J = 8.1Hz), 7.18 (2H, d, J = 8.1Hz), 7.42-7.45 (1H, m), 7.46 (1H, s), 8.19 (3H, brs).

Example 348

4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-2-methoxybenzoic acid dihydrochloride

1) 3-Methoxy-4-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (680 mg, yield 94%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.50 g, 1.22 mmol) and methyl 4-(bromomethyl)-2-methoxybenzoate (315 mg, 1.22 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6Hz), 1.38 (9H, s), 2.16-2.25 (1H, m), 2.33 (3H, s), 2.54 (3H, s), 2.78 (2H, d, J = 7.4Hz), 3.86 (3H, s), 3.90 (3H, s), 4.11-4.13 (2H, m), 4.21 (1H, brs), 4.94 (2H, s), 6.65 (1H, dd, J = 8.0, 1.4 Hz), 6.75 (1H, d, J = 1.1Hz), 6.99 (2H, d, J = 8.1Hz), 7.08 (2H, d, J = 7.7Hz), 7.70 (1H, d, J = 7.9Hz).

2) 4-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-2-methoxybenzoic acid (550 mg, yield 83%) was obtained as a colorless oil from 3-methoxy-4-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (680 mg, 1.15 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.16-2.25 (1H, m), 2.33 (3H, s), 2.54 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 4.04 (3H, s), 4.11-4.13 (2H, m), 4.20 (1H, brs), 4.98 (2H, s), 6.77 (1H, d, J = 9:4 Hz), 6.84 (1H, s), 6.99 (2H, d, J = 8.1 Hz), 7.07 (2H, d, J = 7.9 Hz), 8.08 (1H, d, J = 7.9 Hz).

3) 4-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-

methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-2-methoxybenzoic acid dihydrochloride (240 mg, yield 85%) was obtained as a white solid from 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-2-methoxybenzoic acid (293 mg, 0.509 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.14-2.26 (1H, m), 2.33 (3H, s), 2.58 (3H, brs), 2.93 (2H, brs), 3.78 (3H, s), 3.81 (2H, d, J = 4.5 Hz), 5.01 (2H, s), 6.62 (1H, d, J = 7.9 Hz), 6.92 (1H, d, J = 0.9 Hz), 7.12-7.22 (4H, m), 7.55 (1H, d, J = 7.7 Hz), 8.37 (3H, brs).

Example 349

4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]benzoic acid dihydrochloride

1) 4-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]benzoic acid (182 mg, yield 94%) was obtained as a white powder from methyl 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]benzoate (200 mg, 0.349 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) : 0.92 (6H, d, J = 6.6 Hz), 1.34 (9H, s), 2.10-2.24 (1H, m), 2.35 (3H, s), 2.38 (3H, s), 2.58 (2H, s), 3.22 (2H, s), 3.77 (2H, d, J = 3.0 Hz), 4.20 (1H, brs), 4.27 (2H, d, J = 5.8 Hz), 6.74 (1H, s), 7.09 (2H, d, J = 8.1 Hz), 7.17 (2H, d, J = 8.1 Hz), 7.28 (2H, d, J = 8.3 Hz), 7.90 (2H, d, J = 8.3 Hz), 8.17 (1H, s).

2) 4-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]benzoic acid dihydrochloride (135 mg, yield 95%) was obtained as a white powder from 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-

isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]benzoic acid (150 mg, 0.268 mmol) according to a method similar to the method f Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.07-2.24 (1H, m), 2.40 (3H, s), 2.78 (3H, s), 3.10 (2H, s), 3.41 (2H, s), 3.78 (2H, s), 4.27 (2H, d, J = 5.7 Hz), 7.16 (2H, d, J = 7.9 Hz), 7.26-7.34 (4H, m), 7.92 (2H, d, J = 8.3 Hz), 8.33 (3H, brs), 8.45 (1H, brs).

Example 350

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]isoxazole-4-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]isoxazole-4-carboxamide dihydrochloride (173 mg, yield 76%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and isoxazole-4-carbonyl chloride (100 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 0.99 (6H, d, J = 6.6 Hz), 2.20-2.31 (1H, m), 2.53 (3H, s), 2.94 (2H, s), 3.82 (2H, brs), 7.09 (1H, s), 7.20 (2H, d, J = 8.1 Hz), 7.25 (2H, d, J = 8.1 Hz), 8.28 (3H, brs), 8.73 (1H, brs), 10.59 (1H, brs).

Example 351

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]furan-2-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]furan-2-carboxamide dihydrochloride (190 mg, yield 85%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and furan-2-carbonyl chloride (100 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 1.00 (6H, d, J = 6.6 Hz), 2.09-2.30 (1H,

m), 2.32 (3H, s), 2.58 (3H, s), 3.04 (2H, brs), 3.83 (2H, s), 6.61 (1H, dd, J = 1.8, 3.3 Hz), 7.14 (1H, d, J = 3.3 Hz), 7.21 (2H, d, J = 7.8 Hz), 7.25 (2H, d, J = 7.8 Hz), 7.84 (1H, s), 8.37 (3H, brs), 9.98 (1H, brs).

Example 352

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-methylbenzamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-methylbenzamide dihydrochloride (211 mg, yield 87%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 4-methylbenzoyl chloride (116 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6). : 1.00 (6H, d, J = 6.6 Hz), 2.22-2.32 (1H, m), 2.31 (3H, s), 2.32 (3H, s), 2.57 (3H, s), 3.01 (2H, brs), 3.84 (2H, s), 7.21-7.27 (6H, m), 7.55 (2H, d, J = 8.1 Hz), 8.32 (3H, brs), 9.88 (1H, brs).

Example 353

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-tert-butylbenzamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-tert-butylbenzamide dihydrochloride (211 mg, yield 83%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 4-tert-butylbenzoyl chloride (147 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 1.00 (6H, d, J = 6.6 Hz), 1.27 (9H, s), 2.22-2.31 (1H, m), 2.31 (3H, s), 2.56 (3H, s), 3.01 (2H, brs), 3.84 (2H, s), 7.21-7.26 (4H, m), 7.44 (2H, d, J = 8.4 Hz), 7.60 (2H, d, J = 8.4 Hz), 8.32 (3H, brs), 9.91 (1H, brs).

Example 354

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-chlorobenzamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-chlorobenzamide dihydrochloride (203 mg, yield 82%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 4-chlorobenzoyl chloride (131 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 1.00 (6H, d, J = 6.6 Hz), 2.20-2.30 (1H, m), 2.31 (3H, s), 2.62 (3H, s), 3.08 (2H, brs), 3.86 (2H, s), 7.25 (4H, s), 7.52 (2H, d, J = 8.4 Hz), 7.67 (2H, d, J = 8.4 Hz), 8.41 (3H, brs), 10.20 (1H, brs).

Example 355

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-cyanobenzamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-cyanobenzamide dihydrochloride (209mg, yield 86%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 4-cyanobenzoyl chloride (126mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 1.00 (6H, d, J = 6.6 Hz), 2.10-2.31(1H, m), 2.31 (3H, s), 2.59 (3H, s), 3.02 (2H, brs), 3.85 (2H, s), 7.24 (4H, s), 7.76 (2H, d, J = 8.1 Hz), 7.94 (2H, d, J = 8.1 Hz), 8.36(3H, brs), 10.36 (1H, brs).

Example 356

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-trifluoromethylbenzamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-trifluoromethylbenzamide dihydrochloride (209 mg, yield 86%) was obtained as a white

powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 4-trifluoromethylbenzoyl chloride (156 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 1.00 (6H, d, J = 6.6 Hz), 2.21-2.32 (1H, m), 2.31 (3H, s), 2.55 (3H, s), 2.96 (2H, brs), 3.83 (2H, s), 7.22 (2H, d, J = 7.8 Hz), 7.26 (2H, d, J = 7.8 Hz), 7.78 (2H, d, J = 7.8 Hz), 7.82 (2H, d, J = 7.8 Hz), 8.27 (3H, brs), 10.21 (1H, brs).

Example 357

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]furan-3-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]furan-3-carboxamide dihydrochloride (190 mg, yield 85%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and furan-3-carbonyl chloride (100 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 0.99 (6H, d, J = 6.6 Hz), 2.21-2.32 (1H, m), 2.55 (3H, s), 2.98 (3H, s), 3.82 (2H, brs), 6.74 (1H, s), 7.20 (2H, d, J = 7.8 Hz), 7.25 (2H, d, J = 7.8 Hz), 7.69 (1H, s), 8.15 (1H, s), 8.30 (3H, brs), 9.74 (1H, brs).

Example 358

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]thiophene-3-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]thiophene-3-carboxamide dihydrochloride (233 mg, yield 99%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and thiophene-3-carbonyl chloride (110 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 0.99 (6H, d, J = 6.6 Hz), 2.20-2.31 (1H, m), 2.31 (3H, s), 2.59 (3H, s), 3.05 (2H, brs), 3.84 (2H, s), 7.24 (4H, s), 7.36 (1H, dd, J = 1.2, 5.1 Hz), 7.56 (1H, dd, J = 5.1, 2.7 Hz), 8.10 (1H, d, J = 2.7 Hz), 8.35 (3H, brs), 9.91 (1H, brs).

Example 359

4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-fluorobenzoic acid dihydrochloride

1) 2-Fluoro-4-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (650 mg, yield 92%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.50 g, 1.21 mmol) and methyl 4-(bromomethyl)-3-fluorobenzoate (299 mg, 1.21 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.8 Hz), 1.38 (9H, s), 2.16-2.25 (1H, m), 2.33 (3H, s), 2.54 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.94 (3H, s), 4.09-4.13 (2H, m), 4.20 (1H, brs), 5.05 (2H, s), 6.98-7.09 (5H, m), 7.64-7.71 (2H, m).

2) 4-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-fluorobenzoic acid (450 mg, yield 71%) was obtained as a colorless oil from 2-fluoro-4-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (650 mg, 1.12 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8 Hz), 1.38 (9H, s), 2.13-2.25 (1H, m), 2.33 (3H, s), 2.56 (3H, s), 2.80 (2H, d, J = 7.2 Hz), 4.09-4.16 (2H, m), 4.22 (1H, brs), 5.07 (2H, s), 7.00-7.12 (5H, m), 7.70-7.76 (2H; m).

3) 4-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-fluorobenzoic

acid dihydrochloride (329 mg, yield 76%) was obtained as a white solid from 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-fluorobenzoic acid (450 mg, 0.797 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.95 (6H, d, J = 6.6 Hz), 2.16-2.23 (1H, m), 2.29 (3H, s), 2.86 (2H, brs), 3.78 (2H, d, J = 5.5 Hz), 5.11 (2H, s), 7.07-7.13 (4H, m), 7.18 (1H, t, J = 7.6 Hz), 7.60-7.69 (2H, m), 8.23 (3H, brs).

Example 360

4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-chlorobenzoic acid dihydrochloride

1) 2-Chloro-4-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (518 mg, yield 99%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.36 g, 0.873 mmol) and methyl 4-(bromomethyl)-3-chlorobenzoate (230 mg, 0.873 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8 Hz), 1.38 (9H, s), 2.17-2.26 (1H, m), 2.32 (3H, s), 2.56 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 3.94 (3H, s), 4.11-4.13 (2H, m), 4.22 (1H, brs), 5.11 (2H, s), 7.02-7.04 (3H, m), 7.09 (2H, d, J = 8.1 Hz), 7.78 (1H, dd, J = 8.0, 1.6 Hz), 7.99 (1H, d, J = 1.5 Hz).

2) 4-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-chlorobenzoic acid (420 mg, yield 83%) was obtained as a white solid from 2-chloro-4-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (518 mg, 0.870 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.22-2.33 (4H, m), 2.59 (3H, brs), 2.82 (2H, brs), 4.09-4.17 (2H, m), 4.25 (1H, brs), 5.13 (2H, s), 7.01-7.14 (5H, m), 7.83 (1H, dd, J = 8.0, 1.6 Hz), 8.04 (1H, d, J = 1.5 Hz).

3) 4-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-chlorobenzoic acid dihydrochloride (265 mg, yield 66%) was obtained as a white solid from 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-chlorobenzoic acid (420 mg, 0.722 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.15-2.24 (1H, m), 2.29 (3H, s), 2.54 (3H, s), 2.86 (2H, brs), 3.79 (2H, d, J = 5.3 Hz), 5.14 (2H, s), 7.13 (4H, s), 7.16 (1H, d, J = 7.9 Hz), 7.78 (1H, dd, J = 7.9, 1.5 Hz), 7.90 (1H, d, J = 1.5 Hz), 8.25 (3H, brs).

Example 361

4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]isophthalic acid dihydrochloride

1) Dimethyl 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]isophthalate (1.12 g, yield 99%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.75 g, 1.82 mmol) and dimethyl 4-(bromomethyl)isophthalate (522 mg, 1.82 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.15-2.26 (1H, m), 2.35 (3H, s), 2.57 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 3.91 (3H, s), 3.96 (3H, s), 4.11-4.16 (2H, m), 4.23 (1H, brs), 5.45 (2H, s), 6.99 (1H, d, J = 8.1 Hz), 7.06 (2H, d, J = 8.3 Hz), 7.13 (2H, d, J = 7.9 Hz), 7.99 (1H, dd, J = 8.1, 1.9

Hz), 8.59 (1H, d, J = 1.9 Hz).

2) 4-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]isophtalic acid (750 mg, yield 68%) was obtained as a colorless oil from dimethyl 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]isophthalate (1.12 g, 1.81 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.4 Hz), 1.38 (9H, s), 2.23-2.35 (4H, m), 2.58 (3H, s), 2.86 (2H, d, J = 5.1 Hz), 4.11-4.21 (2H, m), 4.35 (1H, brs), 5.48 (2H, s), 7.01-7.17 (5H, m), 7.96-8.08 (1H, m), 8.64-8.75 (1H, m).

3) 4-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]isophthalic acid dihydrochloride (362 mg, yield 90%) was obtained as a white solid from 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]isophthalic acid (420 mg, 0.711 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 2.16-2.27 (1H, m), 2.33 (3H, s), 2.57 (3H, brs), 2.90 (2H, brs), 3.82 (2H, d, J = 5.1 Hz), 5.42 (2H, s), 7.01 (1H, d, J = 8.1 Hz), 7.19 (2H, d, J = 8.7 Hz), 7.23 (2H, d, J = 8.3 Hz), 7.97 (1H, dd, J = 8.1, 1.9 Hz), 8.31 (3H, brs), 8.42 (1H, d, J = 1.9 Hz).

Example 362

2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N-[4-(dimethylamino)phenyl]acetamide trihydrochloride

1) tert-Butyl {[5-(2-{[4-(dimethylamino)phenyl]amino}-2-oxoethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (450 mg, yield 71%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (500 mg,

1.17 mmol) and 4-(dimethylamino)aniline (500 mg, 3.67 mmol) according to a method similar to the method of Example 311-1).
^{1}H-NMR ($CDCl_3$) : 0.98 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.16-2.27 (1H, m), 2.40 (3H, s), 2.63 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 2.90 (6H, s), 3.42 (2H, s), 4.06 (2H, d, J = 5.1 Hz), 4.20 (1H, brs), 6.58 (1H, brs), 6.66 (2H, d, J = 8.1 Hz), 7.02 (2H, d, J = 7.7 Hz), 7.18 (2H, d, J = 8.1 Hz), 7.24 (2H, d, J = 7.7 Hz).

2) 2-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N-[4-(dimethylamino)phenyl]acetamide trihydrochloride (62 mg, yield 42%) was obtained as a violet powder from tert-butyl {[5-(2-{[4-(dimethylamino)phenyl]amino}-2-oxoethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (100 mg, 0.268 mmol) according to a method similar to the method of Example 2-3).
^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.4 Hz), 2.13-2.28 (1H, m), 2.38 (3H, s), 2.76 (3H, s), 3.01 (6H, s), 3.13 (2H, s), 3.77-3.86 (5H, m), 7.20 (2H, d, J = 8.1 Hz), 7.35 (2H, d, J = 8.1 Hz), 7.51 (2H, d, J = 8.1 Hz), 8.30 (2H, d, J = 8.1 Hz) 8.56 (3H, brs).

Example 363

ethyl 5-(aminomethyl)-4-(4-methylphenyl)-2,6-dineopentylnicotinate

1) A mixture of potassium 3-ethoxy-3-oxopropionate (7.6 g, 45 mmol), magnesium chloride (2.8 g, 30 mmol) and tetrahydrofuran (75 mL) was stirred at 50 C for 4 hrs. The obtained suspension was allowed to cool to room temperature, and a reaction mixture obtained by stirring a mixture of tert-butylacetic acid (3.5 g, 30 mmol), N,N'-carbonyldiimidazole (5.8 g, 36 mmol) and tetrahydrofuran (50 mL) at room temperature for 1 hr was added dropwise to the suspension. The resulting mixture was stirred at room temperature for 3 days. The reaction mixture was partitioned between ethyl acetate and 0.5N hydrochloric acid. The organic layer was washed successively with saturated

aqueous sodium hydrogen carbonate and saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give ethyl 5,5-dimethyl-3-oxohexanoate as a crude product (5.9 g). A mixture of the crude product (5.9 g), ammonium acetate (9.8 g, 127 mmol), acetic acid (1.45 mL, 25 mmol) and toluene (200 mL) was heated under reflux using a Dean-Stark trap for 17 hrs. The reaction mixture was allowed to cool to room temperature, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give ethyl 3-amino-5,5-dimethylhex-2-enoate (2.5 g, yield 52%) as a white powder.

^{1}H-NMR ($CDCl_3$) : 1.00 (9H, s), 1.27 (3H, t, J = 7.2 Hz), 1.98 (2H, s), 4.11 (2H, q, J = 7.2 Hz), 4.45 (2H, brs), 8.05 (1H, s).

2) Ethyl 5-cyano-4-(4-methylphenyl)-2,6-dineopentyl-1,4-dihydropyridine-3-carboxylate (3.5 g, yield 65%) was obtained as a white powder from 5,5-dimethyl-3-oxohexanenitrile (2.4 g, 13 mmol), p-tolualdehyde (1.6 g, 13 mol) and ethyl 3-amino-5,5-dimethylhex-2-enoate (2.5 g, 13 mmol) according to a method similar to the method of Example 1-2).

^{1}H-NMR ($CDCl_3$) : 1.01 (9H, s), 1.03 (9H, s), 1.17 (3H, t, J = 7.2 Hz), 2.06 (1H, d, J = 13.7 Hz), 2.27 (1H, d, J = 13.7 Hz), 2.31 (3H, s), 2.52 (1H, d, J = 13.7 Hz), 3.34 (1H, d, J = 13.7 Hz), 3.95-4.10 (2H, m), 4.63 (1H, s), 5.44 (1H, brs), 7.09 (2H, d, J = 8.0 Hz), 7.17 (2H, d, J = 8.0 Hz).

3) Ethyl 5-cyano-4-(4-methylphenyl)-2,6-dineopentylnicotinate (3.2 g, yield 96%) was obtained as a white powder from ethyl 5-cyano-4-(4-methylphenyl)-2,6-dineopentyl-1,4-dihydropyridine-3-carboxylate (3.4 g, 8.2 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) : 0.91 (3H, t, J = 7.2 Hz), 1.01 (9H, s), 1.08 (9H, s), 2.40 (3H, s), 2.87 (2H, s), 3.02 (2H, s), 3.99 (2H, q,

J = 7.2 Hz), 7.20-7.30 (4H, m).

4) Ethyl 5-(aminomethyl)-4-(4-methylphenyl)-2,6-dineopentylnicotinate (0.91 g, yield 90%) was obtained as a colorless oil from ethyl 5-cyano-4-(4-methylphenyl)-2,6-dineopentylnicotinate (1.0 g, 2.5 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) : 0.89 (3H, t, J = 7.2 Hz), 0.99 (9H, s), 1.04 (9H, s), 1.33 (2H, brs), 2.38 (3H, s), 2.78 (2H, s), 2.88 (2H, s), 3.72 (2H, s), 3.89 (2H, q, J = 7.2 Hz), 7.12 (2H, d, J = 8.0 Hz), 7.20 (2H, d, J = 8.0 Hz).

Example 364

3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}propane-1-ol dihydrochloride

1) A mixture of [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl methanesulfonate (1.91 g, 4.01 mmol), 1,3-propanediol (3.05 g, 40.1 mmol), sodium hydride (60% in oil, 1.60 g, 40.1 mmol) and tetrahydrofuran (5 mL) was stirred at 55 C for 16 hrs. The reaction mixture was allowed to cool to room temperature and 1N hydrochloric acid was added to stop the reaction. The reaction mixture was diluted with ethyl acetate and washed with saturated brine. The organic layer was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl {[5-[(3-hydroxypropoxy)methyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (840 mg, yield 46%) as a white powder.

^{1}H-NMR ($CDCl_3$) : 0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 1.70-1.80 (2H, m), 2.16-2.27 (1H, m), 2.42 (3H, s), 2.63 (3H, s), 2.75 (2H, d, J = 7.4 Hz), 3.40 (2H, t, J = 5.8 Hz), 3.70 (2H, t, J = 5.8 Hz), 4.06 (2H, d, J = 4.7 Hz), 4.10 (2H, s), 4.20 (1H, brs), 7.03 (2H, d, J = 7.9 Hz), 7.24 (2H, d, J = 7.9 Hz).

2) 3-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}propane-1-ol dihydrochloride

(15 mg, yield 100%) was obtained as a white powder from tert-butyl {[5-[(3-hydroxypropoxy)methyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (18 mg, 0.0394 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.4 Hz), 1.70-2.3 (2H, m), 2.38 (3H, s), 2.75 (2H, s), 3.35-4.20 (6H, m), 4.06 (2H, d, J = 4.5 Hz), 4.11 (2H, d, J = 4.5 Hz), 7.00 (2H, d, J = 8.1 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.51 (2H, d, J = 8.1 Hz), 8.56 (3H, brs).

Example 365

4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phthalic acid dihydrochloride

1) Dimethyl 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phthalate (1.68 g, yield 95%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.18 g, 2.86 mmol) and dimethyl 4-(bromomethyl)phthalate (820 mg, 2.86 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.17-2.26 (1H, m), 2.33 (3H, s), 2.54 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 3.92 (3H, s), 3.93 (3H, s), 4.11-4.15 (2H, m), 4.21 (1H, brs), 4.95 (2H, s), 7.00 (2H, d, J = 8.1 Hz), 7.09 (2H, d, J = 7.9 Hz), 7.16 (1H, dd, J = 7.9, 1.7 Hz), 7.47 (1H, d, J = 1.5 Hz), 7.62 (1H, d, J = 7.7 Hz).

2) 4-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phthalic acid (1.60 g, yield 99%) was obtained as a colorless oil from dimethyl 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phthalate (1.68 g, 2.72 mmol) according to a method similar to the method of

Example 9-1).

^{1}H-NMR ($CDCl_3$) :1.00 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.16-2.27 (1H, m), 2.39 (3H, s), 2.67 (3H, brs), 3.10 (2H, d, J = 7.0 Hz), 4.23 (2H, d, J = 4.9 Hz), 4.51 (1H, brs), 5.01 (2H, s), 7.07 (2H, s), 7.21-7.24 (3H, m), 8.03 (1H, s), 8.13 (1H, d, J = 7.9 Hz).

3) 4-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phthalic acid dihydrochloride (396 mg, yield 84%) was obtained as a white solid from 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phthalic acid (0.49 g, 0.830 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.17-2.26 (1H, m), 2.33 (3H, s), 2.56 (3H, brs), 2.91 (2H, brs), 3.81 (2H, d, J = 4.9 Hz), 5.05 (2H, s), 7.13 (2H, d, J = 7.9 Hz), 7.17-7.21 (3H, m), 7.39 (1H, d, J = 1.5 Hz), 7.59 (1H, d, J = 7.9 Hz), 8.32 (3H, brs).

Example 366

4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-2-fluorobenzoic acid dihydrochloride

1) 4-Bromo-3-fluorobenzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.36 g, yield 78%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.20 g, 2.91 mmol) and (4-bromo-3-fluorophenyl)methanol (597 mg, 2.91 mmol) according to a method similar to the method of Example 247-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.16-2.25 (1H, m), 2.36 (3H, s), 2.55 (3H, s), 2.78 (2H, d, J = 7.2 Hz), 4.11-4.16 (2H, m), 4.21 (1H, brs), 4.86 (2H, s), 6.61-6.65 (1H, m), 7.00-7.06 (3H, m), 7.12-7.19 (3H, m).

2) 3-Fluoro-4-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (520 mg, yield 39%) was obtained as a yellow oil from 4-bromo-3-fluorobenzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.36 g, 2.27 mmol) according to a method similar to the method of Example 231-2).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.15-2.25 (1H, m), 2.33 (3H, s), 2.55 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 3.94 (3H, s), 4.09-4.15 (2H, m), 4.21 (1H, brs), 4.94 (2H, s), 6.81-6.85 (1H, m), 7.00 (2H, d, J = 8.1 Hz), 7.10 (2H, d, J = 7.9 Hz), 7.63-7.67 (2H, m).

3) 4-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-2-fluorobenzoic acid (480 mg, yield 94%) was obtained as a colorless oil from 3-fluoro-4-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (520 mg, 0.899 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.16-2.26 (1H, m), 2.33 (3H, s), 2.56 (3H, s), 2.81 (2H, d, J = 7.4 Hz), 4.09-4.16 (2H, m), 4.24 (1H, brs), 4.96 (2H, s), 6.88-6.92 (1H, m), 7.02 (2H, d, J = 7.9 Hz), 7.11 (2H, d, J = 7.9 Hz), 7.69-7.73 (2H, m).

4) 4-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-2-fluorobenzoic acid dihydrochloride (192 mg, yield 42%) was obtained as a white solid from 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-2-fluorobenzoic acid (480 mg, 0.850 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.8 Hz), 2.12-2.26 (1H, m), 2.30 (3H, s), 2.53 (3H, s), 2.86 (2H, d, J = 7.0 Hz), 3.79 (2H,

d, J = 5.7 Hz), 5.05 (2H, s), 7.05-7.16 (5H, m), 7.59-7.64 (2H, m), 8.24 (3H, brs).

Example 367

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide dihydrochloride (172 mg, yield 66%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carbonyl chloride (150 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 1.10 (6H, d, J = 6.6 Hz), 2.00-2.09 (2H, m), 2.11-2.31 (1H, m), 2.31 (3H, s), 2.44 (2H, t, J = 6.3 Hz), 2.59 (3H, s), 2.93 (2H, t, J = 6.3 Hz), 3.06 (2H, s), 3.85 (2H, s), 7.24 (4H, s), 8.35 (1H, s), 8.36 (3H, brs), 11.42 (1H, brs).

Example 368

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-2-phenyl-1,3-thiazole-4-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-2-phenyl-1,3-thiazole-4-carboxamide dihydrochloride (155 mg, yield 57%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 2-phenyl-1,3-thiazole-4-carbonyl chloride (167 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 1.00 (6H, d, J = 6.6 Hz), 2.20-2.29 (1H, m), 2.28 (3H, s), 2.61 (3H, s), 3.04 (2H, s), 3.85 (2H, s), 7.26 (4H, s), 7.53-7.55 (3H, m), 7.95-7.98 (2H, m), 8.35 (1H,

s), 8.36 (3H, brs), 9.85 (1H, brs).

Example 369

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]pyrazine-2-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]pyrazine-2-carboxamide dihydrochloride (157 mg, yield 63%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and pyrazine-2-carbonyl chloride (107 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) : 1.01 (6H, d, J = 6.6 Hz), 2.18-2.28 (1H, m), 2.27 (3H, s), 2.63 (3H, s), 3.12 (2H, s), 3.85 (2H, s), 7.21 (2H, d, J = 8.1 Hz), 7.26 (2H, d, J = 8.1 Hz), 8.46 (3H, brs), 8.70 (1H, s), 8.88 (1H, s), 9.08 (1H, s), 10.48 (1H, brs).

Example 370

4-[({[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetyl}oxy)methyl]benzoic acid dihydrochloride

1) 6N Hydrochloric acid (200 mL) was added to tert-butyl {[5-(cyanomethyl)-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (16 g, 37 mmol) and the mixture was stirred at 90 C for 24 hrs. The reaction mixture was washed with a mixed solvent of tetrahydrofuran-toluene (1:2) and concentrated under reduced pressure. The residue was dissolved in water and alkalified by adding 4N aqueous sodium hydroxide solution. The obtained alkalified solution was washed with ethyl acetate and concentrated under reduced pressure. Tetrahydrofuran (100 mL) and water (50 mL) were added to the residue and the mixture was stirred vigorously. Di-tert-butyl dicarbonate (8.5 mL, 37 mmol) was added dropwise and the mixture was stirred at room temperature for 17 hrs. 1N Hydrochloric acid was added to the

reaction mixture to acidify the aqueous layer and the mixture was extracted with ethyl acetate. The extracts were combined, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was crystallized from hexane-ethyl acetate to give [5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetic acid (13 g, yield 80%) as a white powder.

^{1}H-NMR ($CDCl_3$) : 1.09 (9H, s), 1.39 (9H, s), 2.43 (3H, s), 2.82 (3H, d, J = 20 Hz), 3.34 (2H, brs), 3.43 (2H, brs), 4.05-4.25 (2H, m), 4.35-4.50 (1H, m), 6.97 (2H, dd, J = 7.5, 24 Hz), 7.26 (2H, dd, J = 7.5, 29 Hz),

2) A mixture of [5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetic acid (0.50 g, 1.1 mmol), triethylamine (0.17 mL, 1.3 mmol) and tetrahydrofuran (20 mL) was ice-cooled and a solution of 2,4,6-trichlorobenzoyl chloride (0.31 g, 1.3 mmol) in tetrahydrofuran (2 mL) was added dropwise. The obtained mixture was stirred at room temperature for 14 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), and 2-oxo-2-phenylethyl 4-(hydroxymethyl)benzoate (0.37 g, 1.4 mmol) and 4-dimethylaminopyridine (0.17 g, 1.4 mmol) were added. The obtained solution was stirred at room temperature for 30 min. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed successively with 0.1 M aqueous citric acid solution, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give 2-oxo-2-phenylethyl 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetyl}oxy)methyl]benzoate (0.63 g, yield 80%) as a white powder.

^{1}H-NMR ($CDCl_3$) : 1.02 (9H, s), 1.37 (9H, s), 2.39 (3H, s), 2.49 (3H, s), 2.84 (2H, s), 3.43 (2H, s), 4.08 (2H, d, J = 4.0 Hz), 4.15-4.25 (1H, m), 5.11 (2H, s), 5.59 (2H, s), 6.94 (2H, d, J = 7.9 Hz), 7.17 (2H, d, J = 7.9 Hz), 7.31 (2H, d, J = 8.3 Hz), 7.45-7.55 (2H, m), 7.60-7.70 (1H, m), 7.95-8.00 (2H, m), 8.11 (2H, d, J = 8.3 Hz).

3) 2-Oxo-2-phenylethyl 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetyl}oxy)methyl]benzoate (0.61 g, 0.88 mmol) was dissolved in ethyl acetate (2 mL) and water (2 mL), acetic acid (5 mL) and zinc powder (0.42 g, 6.4 mmol) were successively added to the obtained solution. The resulting mixture was stirred at 55 C for 24 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The obtained residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography and further recrystallized from hexane-ethyl acetate to give 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetyl}oxy)methyl]benzoic acid (0.29 g, yield 48%) as a white powder.

^{1}H-NMR ($CDCl_3$) : 1.02 (9H, s), 1.36 (9H, s), 2.38 (3H, s), 2.47 (3H, s), 2.88 (2H, s), 3.43 (2H, s), 4.10 (2H, d, J = 5.1 Hz), 4.15-4.25 (1H, m), 5.11 (2H, s), 6.94 (2H, d, J = 7.7 Hz), 7.17 (2H, d, J = 7.7 Hz), 7.30 (2H, d, J = 8.1 Hz), 8.07 (2H, d, J = 8.1 Hz).

4) 4-[({[5-(Aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetyl}oxy)methyl]benzoic acid dihydrochloride (0.22 g, yield 92.4%) was obtained as a pale-yellow powder from 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetyl}oxy)methyl]benzoic acid (0.25 g,

0.44 mmol) according to a method similar to the method of Example 276-3).

^{1}H-NMR (DMSO-d_6) : 1.01 (9H, s), 2.37 (3H, s), 2.73 (3H, brs), 3.00-3.30 (2H, m), 3.57 (2H, brs), 3.82 (2H, brs), 5.11 (2H, s), 7.09 (2H, d, J = 7.9 Hz), 7.28 (2H, d, J = 7.9 Hz), 7.34 (2H, d, J = 8.2 Hz), 7.94 (2H, d, J = 8.2 Hz), 8.19 (3H, brs).

Example 371

2-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]furan-3-carboxylic acid dihydrochloride

1) [3-(Methoxycarbonyl)-2-furyl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (320 mg, yield 47%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (0.50 g, 1.22 mmol) and methyl 2-(bromomethyl)furan-3-carboxylate (266 mg, 1.22 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.8 Hz), 1.38 (9H, s), 2.15-2.26 (1H, m), 2.37 (3H, s), 2.55 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.82 (3H, s), 4.09-4.13 (2H, m), 4.19 (1H, brs), 5.27 (2H, s), 6.68 (1H, d, J = 1.9 Hz), 7.00 (2H, d, J = 8.1 Hz), 7.11 (2H, d, J = 7.9 Hz), 7.31 (1H, d, J = 1.9 Hz).

2) 2-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]furan-3-carboxylic acid (310 mg, yield 99%) was obtained as a colorless oil from [3-(methoxycarbonyl)-2-furyl]methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (320 mg, 0.581 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.13-2.22 (1H, m), 2.37 (3H, s), 2.55 (3H, s), 2.80 (2H, d, J = 7.4 Hz), 4.09-4.16 (2H, m), 4.23 (1H, brs), 5.27 (2H, s), 6.72 (1H,

d, J = 1.9 Hz), 7.02 (2H, d, J = 7.9 Hz), 7.13 (2H, d, J = 7.4 Hz), 7.34 (1H, d, J = 1.9 Hz).

3) 2-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]furan-3-carboxylic acid dihydrochloride (241 mg, yield 81%) was obtained as a pale-yellow solid from 2-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]furan-3-carboxylic acid (310 mg, 0.577 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.16-2.25 (1H, m), 2.35 (3H, s), 2.53 (3H, brs), 2.90 (2H, brs), 3.80 (2H, d, J = 5.1 Hz), 5.26 (2H, s), 6.71 (1H, d, J = 1.9 Hz), 7.12 (2H, d, J = 7.9 Hz), 7.19 (2H, d, J = 7.9 Hz), 7.72 (1H, d, J = 1.9 Hz), 8.32 (3H, brs).

Example 372

4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-nitrobenzoic acid dihydrochloride

1) 4-(Methoxycarbonyl)-2-nitrobenzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (1.91 g, yield 63%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.91 g, 4.63 mmol) and methyl 4-(hydroxymethyl)-3-nitrobenzoate (978 mg, 4.63 mmol) according to a method similar to the method of Example 247-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.18-2.28 (1H, m), 2.34 (3H, s), 2.57 (3H, s), 2.79 (2H, d, J = 7.4 Hz), 3.99 (3H, s), 4.10-4.17 (2H, m), 4.23 (1H, brs), 5.41 (2H, s), 7.03-7.09 (3H, m), 7.13 (2H, d, J = 7.9 Hz), 8.08 (1H, dd, J = 8.1, 1.5 Hz), 8.68 (1H, d, J = 1.5 Hz).

2) 4-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-

nitrobenzoic acid (300 mg, yield 93%) was obtained as a colorless oil from 4-(methoxycarbonyl)-2-nitrobenzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (0.33 g, 0.545 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.18-2.34 (4H, m), 2.59 (3H, s), 2.83 (2H, d, J = 6.8 Hz), 4.10-4.18 (2H, m), 4.26 (1H, brs), 5.42 (2H, s), 7.02-7.20 (5H, m), 8.12-8.16 (1H, m), 8.73 (1H, s).

3) 4-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-nitrobenzoic acid dihydrochloride (247 mg, yield 86%) was obtained as a white solid from 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]-3-nitrobenzoic acid (300 mg, 0.507 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.8 Hz), 2.16-2.25 (1H, m), 2.29 (3H, s), 2.60 (3H, brs), 2.94-3.00 (2H, m), 3.81 (2H, d. J = 5.5 Hz), 5.42 (2H, s), 7.17 (4H, s), 7.24 (1H, d, J = 8.1 Hz), 8.13 (1H, dd, J = 8.1, 1.7 Hz), 8.39 (3H, brs), 8.48 (1H, d, J = 1.7 Hz).

Example 373

methyl 3-{[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate dihydrochloride

1) Ethyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate (2.34 g, yield 81%) was obtained as a colorless oil from tert-butyl {[5-(hydroxymethyl)-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (2.09 g, 5.07 mmol) and ethyl 3-hydroxy-1-methyl-1H-pyrazole-4-carboxylate (863 mg, 5.07 mmol) according to a method similar to the method of Example 183-1).

^{1}H-NMR ($CDCl_3$) :1.03 (9H, s), 1.26-1.28 (3H, m), 1.37 (9H, s), 2.36 (3H, s), 2.66 (3H, s), 2.86 (2H, s), 3.68 (3H, s), 4.13 (1H, brs), 4.23 (2H, q, J = 7.1 Hz), 4.90 (2H, s), 7.11 (2H, d, J = 8.3 Hz), 7.16 (2H, d, J = 8.1 Hz), 7.62 (1H, s).

2) 3-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylic acid (2.22 g, yield 99%) was obtained as a colorless oil from ethyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate (2.34 g, 4.14 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :1.04 (9H, s), 1.37 (9H, s), 2.35 (3H, s), 2.66 (3H, s), 2.88 (2H, s), 3.70 (3H, s), 4.09-4.18 (2H, m), 4.24 (1H, brs), 4.95 (2H, s), 7.08 (2H, d, J = 7.5 Hz), 7.18 (2H, d, J = 7.7 Hz), 7.68 (1H, s).

3) Methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate (480 mg, yield 91%) was obtained as a colorless oil from 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylic acid (0.51 g, 0.950 mmol) according to a method similar to the method of Example 305-3).

^{1}H-NMR ($CDCl_3$) :1.03 (9H, s), 1.37 (9H, s), 2.36 (3H, s), 2.66 (3H, s), 2.86 (2H, s), 3.68 (3H, s), 3.76 (3H, s), 4.09-4.17 (2H, m), 4.19 (1H, brs), 4.90 (2H, s), 7.10 (2H, d, J = 8.1 Hz), 7.16 (2H, d, J = 8.1 Hz), 7.62 (1H, s).

4) Methyl 3-{[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate dihydrochloride (349 mg, yield 76%) was obtained as a white solid from methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate (480 mg, 0.872 mmol) according to a method similar

to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.05 (9H, s), 2.38 (3H, s), 2.91 (3H, brs), 3.28 (2H, brs), 3.65 (3H, s), 3.66 (3H, s), 3.89 (2H, brs), 4.90 (2H, s), 7.27 (2H, d, J = 7.9 Hz), 7.33 (2H, d, J = 8.1 Hz), 8.09 (1H, s), 8.32 (3H, brs).

Example 374

3-{[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylic acid dihydrochloride

3-{[5-(Aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylic acid dihydrochloride (210 mg, yield 76%) was obtained as a white solid from 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylic acid (0.29 g, 0.540 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.04 (9H, s), 2.38 (3H, s), 2.87 (3H, brs), 3.23 (2H, brs), 3.64 (3H, s), 3.89 (2H, brs), 4.86 (2H, s), 7.27 (2H, d, J = 7.9 Hz), 7.33 (2H, d, J = 7.9 Hz), 8.00 (1H, s), 8.26 (3H, brs).

Example 375

3-{[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxamide dihydrochloride

1) tert-Butyl {[5-({[4-(aminocarbonyl)-1-methyl-1H-pyrazol-3-yl]oxy}methyl)-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (110 mg, yield 18%) was obtained as a colorless oil from 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylic acid (0.60 g, 1.12 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :1.04 (9H, s), 1.37 (9H, s), 2.37 (3H, s), 2.64 (3H, s), 2.87 (2H, s), 3.69 (3H, s), 4.11-4.16 (2H, m), 4.97

(2H, s), 5.24 (1H, brs), 6.43 (1H, brs), 7.01 (2H, d, J = 7.7 Hz), 7.20 (2H, d, J = 8.3 Hz), 7.69 (1H, s).

2) 3-{[5-(Aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxamide dihydrochloride (70.3 mg, yield 67%) was obtained as a white solid from tert-butyl {[5-({[4-(aminocarbonyl)-1-methyl-1H-pyrazol-3-yl]oxy}methyl)-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (110 mg, 0.205 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.04 (9H, s), 2.38 (3H, s), 2.91 (3H, brs), 3.25 (2H, brs), 3.63 (3H, s), 3.88 (2H, brs), 4.92 (2H, s), 6.35 (1H, brs), 7.09 (1H, brs), 7.27 (2H, d, J = 7.0 Hz), 7.34 (2H, d, J = 7.5 Hz), 7.91 (1H, s), 8.29 (3H, brs).

Example 376

{2-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phenyl}acetic acid dihydrochloride

1) 2-(2-Ethoxy-2-oxoethyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (980 mg, yield 70%) was obtained as a colorless oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (1.00 g, 2.42 mmol) and ethyl [2-(bromomethyl)phenyl]acetate (624 mg, 2.42 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.8 Hz), 1.20 (3H, t, J = 7.2 Hz), 1.38 (9H, s), 2.15-2.26 (1H, m), 2.35 (3H, s), 2.51 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.51 (2H, s), 4.02-4.09 (2H, m), 4.09-4.13 (2H, m), 4.19 (1H, brs), 5.02 (2H, s), 6.99 (2H, d, J = 8.3 Hz), 7.06-7.08 (3H, m), 7.16-7.21 (2H, m), 7.26-7.31 (1H, m).

2) {2-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phenyl}acetic acid (600 mg, yield 62%)

was obtained as a colorless oil from 2-(2-ethoxy-2-oxoethyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (980 mg, 1.71 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.93 (6H, d, J = 6.8 Hz), 1.37 (9H, s), 2.10-2.21 (1H, m), 2.34 (3H, s), 2.49 (3H, s), 2.76 (2H, d, J = 7.2 Hz), 3.53 (2H, s), 4.05-4.13 (2H, m), 4.29 (1H, brs), 5.01 (2H, s), 6.98 (2H, d, J = 8.3 Hz), 7.02-7.11 (3H, m), 7.18-7.32 (3H, m).

3) {2-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phenyl}acetic acid dihydrochloride (125 mg, yield 62%) was obtained as a white solid from {2-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phenyl}acetic acid (210 mg, 0.374 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.16-2.28 (1H, m), 2.36 (3H, s), 2.88 (2H, brs), 3.47 (2H, s), 3.81 (2H, d, J = 5.1 Hz), 4.99 (2H, s), 6.98 (1H, d, J = 7.5 Hz), 7.13-7.32 (7H, m), 8.27 (3H, brs).

Example 377

2-(2-amino-2-oxoethyl)benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride

1) 2-(2-Amino-2-oxoethyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (323 mg, yield 83%) was obtained as a colorless oil from {2-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbonyl}oxy)methyl]phenyl}acetic acid (0.39 g, 0.695 mmol) according to a method similar to the method of Example 3-1):

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.13-2.26 (1H, m), 2.35 (3H, s), 2.50 (3H, s), 2.76 (2H, d, J = 7.4

Hz), 3.47 (2H, s), 4.06-4.13 (2H, m), 4.24 (1H, brs), 5.01 (2H, s), 6.99 (2H, d, J = 8.1 Hz), 7.06-7.10 (3H, m), 7.19-7.35 (3H, m).

2) 2-(2-Amino-2-oxoethyl)benzyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate dihydrochloride (209 mg, yield 68%) was obtained as a white solid from 2-(2-amino-2-oxoethyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinate (323 mg, 0.577 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.96 (6H, d, J = 6.6 Hz), 2.14-2.25 (1H, m), 2.36 (3H, s), 2.55 (3H, s), 2.93 (2H, brs), 3.32 (2H, s), 3.82 (2H, d, J = 5.1 Hz), 5.08 (2H, s), 6.94 (2H, d, J = 7.4 Hz), 7.14-7.30 (7H, m), 7.51 (1H, brs), 8.35 (3H, brs).

Example 378

methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}thiophene-2-carboxylate dihydrochloride

1) Methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}thiophene-2-carboxylate (460 mg, yield 68%) was obtained as a colorless oil from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.50 g, 1.25 mmol) and methyl 3-hydroxythiophene-2-carboxylate (0.20 g, 1.25 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.8 Hz), 1.39 (9H, s), 2.18-2.27 (1H, m), 2.38 (3H, s), 2.72 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.80 (3H, s), 4.06-4.11 (2H, m), 4.20 (1H, brs), 4.79 (2H, s), 6.50 (1H, d, J = 5.5 Hz), 7.06 (2H, d, J = 8.1 Hz), 7.18 (2H, d, J = 7.9 Hz), 7.29 (1H, d, J = 5.5 Hz).

2) Methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}thiophene-2-carboxylate dihydrochloride (126 mg, yield 84%) was obtained as a white

solid from methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}thiophene-2-carboxylate (158 mg, 0.293 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.4 Hz), 2.15-2.28 (1H, m), 2.37 (3H, s), 2.88 (3H, s), 3.11 (2H, brs), 3.71 (3H, s), 3.82 (2H, s), 4.87 (2H, s), 6.86 (1H, d, J = 5.7 Hz), 7.21-7.34 (4H, m), 7.77 (1H, d, J = 5.5 Hz), 8.36 (3H, brs).

Example 379

methyl 4-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-methyl-1,3-thiazole-5-carboxylate dihydrochloride

1) Ethyl 4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-methyl-1,3-thiazole-5-carboxylate (910 mg, yield 96%) was obtained as a colorless oil from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (0.66 g, 1.66 mmol) and ethyl 4-hydroxy-2-methyl-1,3-thiazole-5-carboxylate (0.31 g, 1.66 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.28 (3H, t, J = 7.2 Hz), 1.39 (9H, s), 2.17-2.26 (1H, m), 2.37 (3H, s), 2.53 (3H, s), 2.77 (2H, d, J = 7.2 Hz), 4.08 (2H, d, J = 4.5 Hz), 4.25 (2H, q, J = 7.0 Hz), 5.13 (2H, s), 7.09 (2H, d, J = 8.1 Hz), 7.16 (2H, d, J = 7.9 Hz).

2) 4-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-methyl-1,3-thiazole-5-carboxylic acid (750 mg, yield 87%) was obtained as a colorless oil from ethyl 4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-methyl-1,3-thiazole-5-carboxylate (910 mg, 1.60 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :1.01 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.18-

2.30 (1H, m), 2.38 (3H, s), 2.57 (3H, s), 2.81 (3H, brs), 2.95 (2H, d, J = 7.0 Hz), 4.09-4.15 (2H, m), 4.31 (1H, brs), 5.22 (2H, s), 7.05 (2H, d, J = 7.9 Hz), 7.22 (2H, d, J = 7.9 Hz).

3) Methyl 4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-methyl-1,3-thiazole-5-carboxylate (420 mg, yield 77%) was obtained as a pale-yellow solid from 4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-methyl-1,3-thiazole-5-carboxylic acid (530 mg, 0.982 mmol) according to a method similar to the method of Example 305-3).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.15-2.27 (1H, m), 2.37 (3H, s), 2.54 (3H, s), 2.68 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.79 (3H, s), 4.08 (2H, d, J = 4.9 Hz), 4.21 (1H, brs), 5.14 (2H, s), 7.09 (2H, d, J = 8.1 Hz), 7.16 (2H, d, J = 7.9 Hz).

4) Methyl 4-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-methyl-1,3-thiazole-5-carboxylate dihydrochloride (342 mg, yield 85%) was obtained as a pale-yellow solid from methyl 4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-methyl-1,3-thiazole-5-carboxylate (420 mg, 0.759 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.13-2.28 (1H, m), 2.38 (3H, s), 2.55 (3H, s), 2.93 (3H, brs), 3.13 (2H, brs), 3.70 (3H, s), 3.80 (2H, brs), 5.17 (2H, s), 7.20-7.26 (2H, m), 7.31 (2H, d, J = 7.4 Hz), 8.38 (3H, brs).

Example 380

4-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-methyl-1,3-thiazole-5-carboxylic acid dihydrochloride

4-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-methyl-1,3-thiazole-5-

carboxylic acid dihydrochloride (145 mg, yield 69%) was obtained as a white solid from 4-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-2-methyl-1,3-thiazole-5-carboxylic acid (220 mg, 0.408 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.15-2.28 (1H, m), 2.38 (3H, s), 2.53 (3H, s), 2.90 (3H, brs), 3.10 (2H, brs), 3.75-3.85 (2H, m), 5.11 (2H, s), 7.25 (2H, d, J = 6.4 Hz), 7.32 (2H, d, J = 7.7 Hz), 8.15-8.42 (3H, m).

Example 381

3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-(carboxymethyl)-1H-pyrazole-4-carboxylic acid dihydrochloride

1) Ethyl 1-acetyl-3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1H-pyrazole-4-carboxylate (1.12 g, yield 77%) was obtained as a white solid from tert-butyl {[5-(hydroxymethyl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (1.00 g, 2.51 mmol) and ethyl 1-acetyl-3-hydroxy-1H-pyrazole-4-carboxylate (597 mg, 3.01 mmol) according to a method similar to the method of Example 214-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.8 Hz), 1.31 (3H, t, J = 7.2 Hz), 1.39 (9H, s), 2.14-2.27 (1H, m), 2.36 (3H, s), 2.51 (3H, s), 2.67 (3H, s), 2.78 (2H, d, J = 7.4 Hz), 4.09 (2H, d, J = 5.1 Hz), 4.20 (1H, brs), 4.28 (2H, q, J = 7.1 Hz), 5.01 (2H, s), 7.09 (2H, d, J = 8.1 Hz), 7.17 (2H, d, J = 7.9 Hz), 8.49 (1H, s).

2) To a solution of ethyl 1-acetyl-3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1H-pyrazole-4-carboxylate (0.86 g, 1.49 mmol) in tetrahydrofuran (10 mL) - methanol (5 mL) was added saturated aqueous sodium hydrogen carbonate (10 mL) and the mixture was stirred at room temperature for 30 min.

The reaction mixture was diluted with ethyl acetate, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give ethyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1H-pyrazole-4-carboxylate (798 mg, yield 99%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) :0.91 (3H, d, J = 6.6 Hz), 0.97 (3H, d, J = 6.6 Hz), 1.24-1.29 (3H, m), 1.40-1.46 (9H, m), 2.19-2.28 (1H, m), 2.36 (3H, brs), 2.65-2.78 (5H, m), 3.87-4.04 (2H, m), 4.08-4.35 (5H, m), 4.87 (1H, brs), 6.91-7.01 (2H, m), 7.07-7.15 (2H, m), 7.84 (1H, s).

3) To a solution of ethyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1H-pyrazole-4-carboxylate (1.09 g, 2.03 mmol) in N,N-dimethylformamide (20 mL) was added sodium hydride (60% in oil, 98 mg, 2.44 mmol) and the mixture was stirred at room temperature for 30 min. tert-Butyl bromoacetate (0.36 mL, 2.44 mmol) was added to the reaction mixture and the mixture was stirred with heating at 60 C for 30 min. The reaction mixture was diluted with ethyl acetate, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give ethyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-(2-tert-butoxy-2-oxoethyl)-1H-pyrazole-4-carboxylate (960 mg, yield 72%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.28 (3H, t, J = 7.1 Hz), 1.39 (9H, s), 1.44 (9H, s), 2.14-2.25 (1H, m), 2.36 (3H, s), 2.66 (3H, s), 2.76 (2H, d, J = 7.4 Hz), 4.08 (2H, d, J = 4.9 Hz), 4.17-4.27 (3H, m), 4.52 (2H, s), 4.91 (2H, s), 7.09

(2H, d, J = 8.1 Hz), 7.16 (2H, d, J = 8.1 Hz), 7.73 (1H, s).

4) To a mixed solution of ethyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-(2-tert-butoxy-2-oxoethyl)-1H-pyrazole-4-carboxylate (960 mg, 1.48 mmol) in tetrahydrofuran (15 mL)-methanol (10 mL) was added 1N aqueous sodium hydroxide solution (10 mL) and the mixture was heated under reflux for 1 hr. The reaction mixture was allowed to cool to room temperature and acidified with 0.5N hydrochloric acid. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-(carboxymethyl)-1H-pyrazole-4-carboxylic acid (838 mg, yield 99%) as an oil. 3-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-(carboxymethyl)-1H-pyrazole-4-carboxylic acid dihydrochloride (58.2 mg, yield 59%) was obtained as a white solid from the obtained oil (107 mg, 0.189 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.14-2.28 (1H, m), 2.38 (3H, s), 2.82 (3H, brs), 3.04 (2H, brs), 3.76-3.86 (2H, m), 4.77 (2H, s), 4.86 (2H, s), 7.26 (2H, d, J = 8.1 Hz), 7.32 (2H, d, J = 7.9 Hz), 8.04 (1H, s), 8.27 (3H, brs).

Example 382

methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-(2-methoxy-2-oxoethyl)-1H-pyrazole-4-carboxylate dihydrochloride

1) Methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-(2-methoxy-2-oxoethyl)-1H-pyrazole-4-carboxylate (560 mg, 0.636 mmol) was obtained as a colorless oil from 3-{[5-{[(tert-

butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-(carboxymethyl)-1H-pyrazole-4-carboxylic acid (870 mg, 1.48 mmol) according to a method similar to the method of Example 305-3).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.15-2.25 (1H, m), 2.36 (3H, s), 2.66 (3H, s), 2.76 (2H, d, J = 7.2 Hz), 3.76 (3H, s), 3.77 (3H, s), 4.08 (2H, d, J = 4.7 Hz), 4.22 (1H, brs), 4.65 (2H, s), 4.91 (2H, s), 7.08 (2H, d, J = 8.1 Hz), 7.16 (2H, d, J = 7.9 Hz), 7.74 (1H, s).

2) Methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-(2-methoxy-2-oxoethyl)-1H-pyrazole-4-carboxylate dihydrochloride (59.8 mg, yield 63%) was obtained as a white solid from methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-(2-methoxy-2-oxoethyl)-1H-pyrazole-4-carboxylate (98.7 mg, 0.166 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.15-2.28 (1H, m), 2.37 (3H, s), 2.74 (3H, brs), 2.94 (2H, brs), 3.67 (3H, s), 3.68 (3H, s), 4.86 (2H, s), 4.91 (2H, s), 7.23 (2H, d, J = 8.1 Hz), 7.29 (2H, d, J = 8.1 Hz), 8.09-8.19 (4H, m).

Example 383

[3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-4-(methoxycarbonyl)-1H-pyrazol-1-yl]acetic acid dihydrochloride

1) To a solution of methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-(2-methoxy-2-oxoethyl)-1H-pyrazole-4-carboxylate (0.46 g, 0.775 mmol) in tetrahydrofuran was added 1N aqueous sodium hydroxide solution (1 mL) and the mixture was stirred at room temperature for 30 min. The reaction mixture was acidified with 0.5N hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate.

The solvent was evaporated under reduced pressure to give [3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-4-(methoxycarbonyl)-1H-pyrazol-1-yl]acetic acid (450 mg, yield 99%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) :1.03 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.21-2.34 (1H, m), 2.43 (3H, s), 3.02-3.26 (5H, m), 3.76 (3H, s), 4.13-4.19 (2H, m), 4.62 (2H, s), 4.99-5.11 (2H, m), 7.12 (2H, d, J = 7.0 Hz), 7.30 (2H, d, J = 7.5 Hz), 7.68-7.75 (1H, m).

2) [3-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-4-(methoxycarbonyl)-1H-pyrazol-1-yl]acetic acid dihydrochloride (42.4 mg, yield 44%) was obtained as a white solid from [3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-4-(methoxycarbonyl)-1H-pyrazol-1-yl]acetic acid (100 mg, 0.172 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.14-2.28 (1H, m), 2.38 (3H, s), 2.85 (3H, brs), 3.07 (2H, brs), 3.68 (3H, s), 3.75-3.85 (2H, m), 4.78 (2H, s), 4.90 (2H, s), 7.25 (2H, d, J = 7.9 Hz), 7.31 (2H, d, J = 7.9 Hz), 8.12 (1H, s), 8.31 (3H, brs).

Example 384

methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-(2-amino-2-oxoethyl)-1H-pyrazole-4-carboxylate dihydrochloride

1) Methyl 1-(2-amino-2-oxoethyl)-3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1H-pyrazole-4-carboxylate (150 mg, yield 37%) was obtained as a white solid from [3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-4-(methoxycarbonyl)-1H-pyrazol-1-yl]acetic acid (400 mg, 0.689 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.18-2.29 (1H, m), 2.36 (3H, s), 2.68 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.78 (3H, s), 4.08 (2H, d, J = 5.1 Hz), 4.22 (1H, brs), 4.54 (2H, s), 4.94 (2H, s), 7.09 (2H, d, J = 8.1 Hz), 7.16 (2H, d, J = 7.9 Hz), 7.74 (1H, s).

2) Methyl 3-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-(2-amino-2-oxoethyl)-1H-pyrazole-4-carboxylate dihydrochloride (141 mg, yield 98%) was obtained as a white solid from methyl 1-(2-amino-2-oxoethyl)-3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1H-pyrazole-4-carboxylate (150 mg, 0.259 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.14-2.27 (1H, m), 2.39 (3H, s), 2.86 (3H, brs), 3.09 (2H, brs), 3.67 (3H, s), 3.81 (2H, d, J = 4.7 Hz), 4.58 (2H, s), 4.89 (2H, s), 7.26 (2H, d, J = 8.1 Hz), 7.32 (2H, d, J = 8.1 Hz), 7.58 (1H, s), 8.33 (3H, brs).

Example 385

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]terephthalamide dihydrochloride

1) tert-Butyl {[5-{[4-(aminocarbonyl)benzoyl]amino}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (248 mg, yield 98%) was obtained as a white powder from 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoic acid (260 mg, 0.48 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.15-2.29 (1H, m), 2.34 (3H, s), 2.50 (3H, s), 2.79 (2H, brs), 4.13 (2H, brs), 4.37 (1H, brs), 5.84 (1H, brs), 6.33 (1H, brs), 7.05 (2H, d, J = 8.1 Hz), 7:19 (2H, d, J = 8.1 Hz), 7.37 (1H, brs), 7.47 (2H, d, J = 8.1 Hz), 7.73 (2H, d, J = 8.1 Hz).

2) N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-

methylphenyl)pyridin-3-yl]terephthalamide dihydrochloride (233 mg, yield 99%) was obtained as a white powder from tert-butyl {[5-{[4-(aminocarbonyl)benzoyl]amino}-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (248 mg, 0.47 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.01 (6H, d, J = 6.3 Hz), 2.19-2.31 (1H, m), 2.31 (3H, s), 2.61 (3H, s), 3.05 (2H, brs), 3.85 (2H, brs), 7.25 (4H, s), 7.51 (1H, brs), 7.68 (2H, d, J = 8.1 Hz), 7.89 (2H, d, J = 8.1 Hz), 8.09 (1H, brs), 8.37 (3H, brs), 10.16 (1H, brs).

Example 386

ethyl 1-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)piperidine-4-carboxylate dihydrochloride

1) Ethyl 1-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)piperidine-4-carboxylate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and ethyl isonipecotate (314 mg, 2.0 mmol) according to a meth d similar to the method of Example 95-1).

EIMS(M+1):567

2) Ethyl 1-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)piperidine-4-carboxylate dihydrochloride (324 mg, yield 69%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.3 Hz), 1.20 (3H, t, J = 6.9 Hz), 1.54-1.59 (2H, m), 2.10-2.28 (1H, m), 2.34 (3H, s), 2.36-2.46 (1H, m), 2.62-2.76 (4H, m), 3.09 (2H, brs), 3.74-3.82 (4H, m), 4.07 (2H, q, J = 6.9 Hz), 7.19 (2H, d, J = 7.5 Hz), 7.26 (2H, d, J = 7.5 Hz), 8.17 (1H, brs), 8.45 (3H, brs).

Example 387

ethyl 2-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-

methylphenyl)pyridin-3-yl]amino}carbonyl)amino]-1,3-oxazole-4-carboxylate dihydrochloride

1) Ethyl 2-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)amino]-1,3-oxazole-4-carboxylate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and ethyl 2-amino-1,3-oxazole-4-carboxylate (312 mg, 2.0 mmol) according to a method similar to the method of Example 95-1).

EIMS(M+1):566

2) Ethyl 2-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)amino]-1,3-oxazole-4-carboxylate dihydrochloride (224 mg, yield 48%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 1.29 (3H, t, J = 7.2 Hz), 2.13-2.26 (1H, m), 2.29 (3H, s), 2.63 (3H, s), 3.06 (2H, brs), 3.82 (2H, s), 4.27 (2H, q, J = 7.2 Hz), 7.15-7.29 (4H, m), 8.44 (3H, brs), 8.45 (1H, s), 9.32 (1H, brs), 11.14 (1H, brs).

Example 388

ethyl 2-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)amino]-1,3-thiazole-4-carboxylate dihydrochloride

1) Ethyl 2-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)amino]-1,3-thiazole-4-carboxylate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and ethyl 2-amino-1,3-thiazole-4-carboxylate (344 mg, 2.0 mmol) according to a method similar to the method of Example 95-1).

EIMS(M+1):582

2) Ethyl 2-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)amino]-1,3-thiazole-4-carboxylate dihydrochloride (282 mg, yield 51%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 1.27 (3H, t, J = 7.2 Hz), 2.11-2.30 (1H, m), 2.35 (3H, s), 2.62 (3H, s), 3.06 (2H, brs), 3.81 (2H, s), 4.24 (2H, q, J = 7.2 Hz), 7.21 (2H, d, J = 7.8 Hz), 7.30 (2H, d, J = 7.8 Hz), 7.91 (1H, s), 8.42 (3H, s), 8.76 (1H, brs), 11.21 (1H, brs).

Example 389

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-phenylpiperidine-1-carboxamide dihydrochloride

1) tert-Butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{[(4-phenylpiperidin-1-yl)carbonyl]amino}pyridin-3-yl)methyl]carbamate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and 4-phenylpiperidine (322 mg, 2.0 mmol) according to a method similar to the method of Example 95-1).

EIMS(M+1):571

2) N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-4-phenylpiperidine-1-carboxamide dihydrochloride (240 mg, yield 44%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 1.54-1.58 (2H, m), 2.14-2.26 (1H, m), 2.26 (3H, s), 2.50 (3H, s), 2.58-2.75 (5H, m), 3.12 (2H, brs), 3.82 (2H, brs), 3.95-3.99 (2H, m), 7.11-7.37 (9H, m), 8.19 (1H, brs), 8.44 (1H, brs).

Example 390

methyl 1-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)pyrrolidine-2-

carboxylate dihydrochloride

1) Methyl 1-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)pyrrolidine-2-carboxylate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and DL-proline methyl ester (286 mg, 2.0 mmol) according to a method similar to the method of Example 95-1).

EIMS(M+1):539

2) Methyl 1-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)pyrrolidine-2-carboxylate dihydrochloride (400 mg, yield 78%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6).:0.98 (6H, d, J = 6.6 Hz), 1.80 (3H, brs), 2.04-2.09 (1H, m), 2.11-2.23 (1H, m), 2.39 (3H, s), 2.63 (2H, s), 3.07 (4H, brs), 3.59 (3H, s), 3.86 (2H, brs), 4.11-4.17 (1H, m), 4.11-4.17 (1H, m), 7.21 (2H, d, J = 7.8 Hz), 7.32 (2H, d, J = 7.8 Hz), 7.93 (1H, brs), 8.39 (3H, brs).

Example 391

ethyl 1-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)piperidine-3-carboxylate dihydrochloride

1) Ethyl 1-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)piperidine-3-carboxylate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and ethyl 3-piperidinecarboxylate (314 mg, 2.0 mmol) according to a method similar to the method of Example 95-1).

EIMS(M+1):567

2) Ethyl 1-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)piperidine-3-carboxylate dihydrochloride (256 mg, yield 48%) was obtained as

a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 1.19 (3H, t, J = 6.9 Hz), 1.39-1.46 (2H, m), 1.78 (2H, brs), 2.16-2.23 (1H, m), 2.37 (3H, s), 2.57 (2H, s), 3.03 (2H, s), 3.66-3.72 (1H, m), 3.82 (2H, brs), 4.05 (2H, q, J = 6.9 Hz), 7.17 (2H, d, J = 8.1 Hz), 7.30 (2H, d, J = 8.1 Hz), 8.11 (1H, brs), 8.29 (3H, brs).

Example 392

2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]tetrahydroimidazo[1,5-a]pyridine-1,3(2H,5H)-dione dihydrochloride

1) tert-Butyl {[5-(1,3-dioxohexahydroimidazo[1,5-a]pyridin-2(3H)-yl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and ethyl 2-piperidinecarboxylate (314 mg, 2.0 mmol) according to a method similar to the method of Example 95-1).

EIMS(M+1):553

2) 2-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]tetrahydroimidazo[1,5-a]pyridine-1,3(2H,5H)-dione dihydrochloride (282 mg, yield 57%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 1.20-1.35 (1H, m), 1.36-1.50 (1H, m), 1.59-1.65 (1H, m), 1.79 (1H, brs), 1.99 (1H, brs), 2.22-2.31 (1H, m), 2.32 (6H, s), 2.35 (3H, s), 2.70-2.74 (1H, m), 2.82 (2H, d, J = 6.9 Hz), 3.72-3.78 (4H, m), 7.05-7.09 (2H, m), 7.10-7.27 (2H, m), 8.13 (3H, brs).

Example 393

2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-10,10a-dihydroimidazo[1,5-b]isoquinoline-1,3(2H,5H)-dione dihydrochloride

1) tert-Butyl {[5-(1,3-dioxo-1,5,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-2(3H)-yl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (410 mg, 2.0 mmol) according to a method similar to the method of Example 95-1).

EIMS(M+1):569

2) 2-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-10,10a-dihydroimidazo[1,5-b]isoquinoline-1,3(2H,5H)-dione dihydrochloride (368 mg, yield 68%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.18-2.34 (1H, m), 2.30 (3H, s), 2.34 (3H, s), 2.34 (2H, d, J = 7.2 Hz), 2.95 (1H, dd, J = 9.9, 17.1 Hz), 3.16 (1H, dd, J = 4.8, 15.6 Hz), 3.78 (2H, m), 4.06 (1H, dd, J = 9.9, 4.8 Hz), 4.08 (1H, d, J = 17.1 Hz), 4.79 (1H, d, J = 15.6 Hz), 7.07-7.31 (8H, m), 8.18 (3H, brs).

Example 394

methyl 2-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoate dihydrochloride

Methyl 2-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoate dihydrochloride (230 mg, yield 89%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and methyl 2-(chlorocarbonyl)benzoate (149 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.18-2.27 (1H, m), 2.40 (3H, s), 2.66 (3H, s), 2.95 (2H, brs), 3.77 (3H, s), 3.79

(2H, brs), 6.58 (1H, d, J = 7.5 Hz), 7.23 (2H, d, J = 7.8 Hz), 7.34 (2H, d, J = 7.8 Hz), 7.49 (1H, t, J = 7.5 Hz), 7.53 (1H, t, J = 7.5 Hz), 7.70 (1H, d, J = 7.5 Hz), 8.25 (3H, brs), 10.03 (1H, brs).

Example 395

2-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoic acid dihydrochloride

1) 2-({[5-({[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoic acid (247 mg, yield 98%) was obtained as a white powder from methyl 2-({[5-({[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoate (260 mg, 0.48 mmol) according to a method similar to the method of Example 36-1)..

^{1}H-NMR ($CDCl_3$) :0.92 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.04-2.18 (1H, m), 2.41 (3H, s), 2.55 (3H, s), 2.82 (2H, brs), 4.09 (3H, brs), 6.17 (1H, brs), 6.91 (1H, brs), 7.09 (2H, brs), 7.25-7.27 (3H, m), 7.37 (1H, brs), 7.88 (1H, brs).

2) 2-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoic acid dihydrochloride (220 mg, yield 94%) was obtained as a white powder from 2-({[5-({[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoic acid (247 mg, 0.47 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.18-2.26 (1H, m), 2.43 (3H, s), 2.74 (3H, s), 3.05 (2H, brs), 3.86 (2H, brs), 6.38 (1H, d, J = 6.9 Hz), 7.25 (2H, d, J = 8.1 Hz), 7.37 (2H, d, J = 8.1 Hz), 7.41 (1H, t, J = 6.9 Hz), 7.49 (1H, t, J = 6.9 Hz), 7.76 (1H, d, J = 6.9 Hz), 8.35 (3H, brs), 10.02 (1H, brs).

Example 396

2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-1H-isoindole-1,3(2H)-dione

dihydrochloride

1) tert-Butyl {[5-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (221 mg, yield 94%) was obtained as a white powder from 2-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)benzoic acid (260 mg, 0.48 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :1.03 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.02 (3H, s), 2.21-2.31 (1H, m), 2.40 (3H, s), 2.83 (2H, d, J = 7.5 Hz), 4.20 (2H, d, J = 5.4 Hz), 4.30 (1H, brs), 6.98 (2H, d, J = 8.1 Hz), 7.03 (2H, d, J = 8.1 Hz), 7.67-7.72 (2H, m), 7.75-7.79 (2H, m).

2) 2-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-1H-isoindole-1,3(2H)-dione dihydrochloride (213 mg, yield 99%) was obtained as a white powder from tert-butyl {[5-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (221 mg, 0.45 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.01 (6H, d, J = 6.3 Hz), 2.19 (3H, s), 2.19-2.32 (1H, m), 2.35 (3H, s), 2.83 (2H, d, J = 6.3 Hz), 3.69 (2H, brs), 7.05 (2H, d, J = 7.8 Hz), 7.13 (2H, d, J = 7.8 Hz), 7.85 (4H, brs), 8.03 (3H, brs).

Example 397

methyl 3-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)oxy]benzoate dihydrochloride

1) Methyl 3-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)oxy]benzoate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nic tinic acid (412 mg, 1.0 mmol) and methyl 3-hydroxybenzoate (304 mg, 2.0 mmol) according to a method

similar to the method of Example 95-1).

EIMS(M+1):562

2) Methyl 3-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)oxy]benzoate dihydrochloride (172 mg, yield 32%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.14-2.28 (1H, m), 2.44 (3H, s), 2.67 (3H, s), 3.02 (2H, s), 3.85 (2H, s), 3.89 (3H, s), 7.26 (2H, d, J = 8.1 Hz), 7.36 (1H, s), 7.39 (2H, d, J = 8.1 Hz), 7.53 (1H, t, J = 7.8 Hz), 7.80 (1H, d, J = 7.8 Hz), 8.37 (3H, brs), 9.75 (1H, brs).

Example 398

methyl 4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)oxy]benzoate dihydrochloride

1) Methyl 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)oxy]benzoate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and methyl 4-hydroxybenzoate (304 mg, 2.0 mmol) according to a method similar to the method of Example 95-1).

EIMS(M+1):562

2) Methyl 4-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)oxy]benzoate dihydrochloride (182 mg, yield 34%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.14-2.29 (1H, m), 2.43 (3H, s), 2.62 (3H, s), 2.93 (2H, brs), 3.84 (2H, s), 3.85 (3H, s), 7.00 (2H, d, J = 8.7 Hz), 7.24 (2H, d, J = 8.1 Hz), 7.39 (2H, d, J = 8.1 Hz), 7.96 (2H, t, J = 8.7 Hz), 8.29 (3H, brs), 9.71 (1H, brs).

Example 399

methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbamate dihydrochloride

1) Methyl 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbamate was obtained as an oil from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and methanol (62 mg, 2.0 mmol) according to a method similar to the method of Example 95-1).

EIMS(M+1):443

2) Methyl 5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]carbamate dihydrochloride (330 mg, yield 80%) was obtained as a white powder from the oil obtained in the aforementioned 1), according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.11-2.18 (1H, m), 2.39 (3H, s), 2.63 (3H, s), 3.11 (2H, s), 3.48 (3H, s), 3.82 (2H, s), 7.18 (2H, d, J = 7.8 Hz), 7.33 (2H, d, J = 7.8 Hz), 8.44 (3H, brs), 9.03 (1H, brs).

Example 400

ethyl (3-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-2,4-dioxoimidazolidin-1-yl)acetate dihydrochloride

1) Diethyl 2,2'-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)imino]diacetate was obtained as white crystals (260 mg, yield 43%) from 5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid (412 mg, 1.0 mmol) and diethyl 2,2'-iminodiacetate (380 mg, 2.0 mmol) according to a method similar to the method of Example 95-1).

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.24 (6H, t, J = 6.9 Hz), 1.38 (9H, s), 2.09-2.24 (1H, m), 2.40 (3H, s), 2.49 (3H, s), 2.75 (2H, d, J = 6.9 Hz), 3.87 (4H, s), 4.12 (4H, q, J =

6.9 Hz), 4.23 (1H, brs), 6.33 (1H, brs), 7.04 (2H, d, J = 7.8 Hz), 7.25 (2H, d, J = 7.8 Hz).

2) Ethyl {3-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-2,4-dioxoimidazolidin-1-yl}acetate dihydrochloride (240 mg, yield 98%) was obtained as a white powder from diethyl 2,2'-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)imino]diacetate (260 mg, 0.43 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 1.19 (6H, t, J = 7.2 Hz), 2.22-2.35 (1H, m), 2.35 (3H, s), 2.50 (3H, s), 2.86 (2H, d, J = 7.2 Hz), 3.74-3.80 (3H, m), 4.02-4.17 (5H, m), 7.04-7.11 (2H, m), 7.21-7.27 (2H, m), 8.25 (3H, brs).

Example 401

ethyl 6-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)pyridine-2-carboxylate dihydrochloride

Ethyl 6-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)pyridine-2-carboxylate dihydrochloride (230 mg, yield 89%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and ethyl 6-(chlorocarbonyl)pyridine-2-carboxylate (149 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 1.35 (3H, t, J = 7.2 Hz), 2.11-2.28 (1H, m), 2.27 (3H, s), 2.60 (3H, s), 3.05 (2H, brs), 3.84 (2H, brs), 4.37 (2H, q, J = 7.2 Hz), 7.22 (1H, d, J = 7.8 Hz), 7.26 (2H, d, J = 7.8 Hz), 8.21-8.31 (3H, m), 8.38 (3H, brs), 9.90 (1H, brs).

Example 402

6-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)pyridine-2-carboxylic

acid dihydrochloride

1) 6-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)pyridine-2-carboxylic acid (247 mg, yield 98%) was obtained as a white powder from ethyl 6-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)pyridine-2-carboxylate (260 mg, 0.48 mmol) according to a method similar to the method of Example 36-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.14-2.26 (1H, m), 2.28 (3H, s), 2.52 (3H, s), 2.84 (2H, brs), 4.15 (2H, s), 4.42 (1H, brs), 7.01 (2H, d, J = 7.8 Hz), 7.10 (2H, d, J = 7.8 Hz), 7.99 (1H, brs), 8.21-8.31 (2H, m), 9.36 (1H, brs).

2) 6-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)pyridine-2-carboxylic acid dihydrochloride (221 mg, yield 94%) was obtained as a white powder from 6-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)pyridine-2-carboxylic acid (247 mg, 0.47 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.11-2.29 (1H, m), 2.25 (3H, s), 2.60 (3H, s), 3.04 (2H, brs), 3.85 (2H, brs), 7.19 (1H, d, J = 7.8 Hz), 7.26 (2H, d, J = 7.8 Hz), 8.17-8.26 (3H, m), 8.37 (3H, brs), 10.67 (1H, brs).

Example 403

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]pyridine-2,6-dicarboxamide dihydrochloride

1) tert-Butyl {[5-({[6-(aminocarbonyl)pyridin-2-yl]carbonyl}amino)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (221 mg, yield 94%) was obtained as a white powder from 6-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]amino}carbonyl)pyridine-2-carboxylic

acid (260 mg, 0.48 mmol) according to a method similar to the method of Example 3-1).

^{1}H-NMR ($CDCl_3$) :1.00 (6H, d, J = 6.6 Hz), 1.39 (9H, s), 2.18-2.29 (1H, m), 2.35 (3H, s), 2.57 (3H, s), 2.79 (2H, d, J = 7.5 Hz), 4.15 (2H, brs), 4.29 (1H, brs), 5.53 (1H, brs), 6.75 (1H, brs), 7.07 (2H, d, J = 7.8 Hz), 7.19 (2H, d, J = 7.8 Hz), 8.02 (1H, t, J = 7.8 Hz), 8.29 (1H, dd, J = 1.2, 7.8 Hz), 8.31 (1H, dd, J = 1.2, 7.8 Hz), 8.74 (1H, s).

2) N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]pyridine-2,6-dicarboxamide dihydrochloride (206 mg, yield 94%) was obtained as a white powder from tert-butyl {[5-({[6-(aminocarbonyl)pyridin-2-yl]carbonyl}amino)-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (221 mg, 0.45 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.3 Hz), 2.12-2.28 (1H, m), 2.25 (3H, s), 2.63 (3H, s), 3.07 (2H, brs), 3.86 (2H, brs), 7.19 (2H, d, J = 7.8 Hz), 7.28 (2H, d, J = 7.8 Hz), 7.76 (1H, s), 8.08-8.20 (3H, m), 8.43 (3H, brs), 8.80 (1H, s), 10.77 (1H, brs).

Example 404

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-1-benzyl-4-methoxy-1H-pyrazole-3-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-1-benzyl-4-methoxy-1H-pyrazole-3-carboxamide dihydrochloride (230 mg, yield 81%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 1-benzyl-4-methoxy-1H-pyrazole-3-carbonyl chloride (188 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.18-2.26 (1H, m), 2.35 (3H, s), 2.51 (3H, s), 2.91 (2H, brs), 3.67 (3H, s), 3.81 (2H, brs),

5.15 (2H, s), 7.16-7.39 (9H, m), 8.11 (1H, s), 8.21 (3H, brs).

Example 405

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-1,5-dimethyl-1H-pyrazole-3-carboxamide dihydrochloride

N-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-1,5-dimethyl-1H-pyrazole-3-carboxamide dihydrochloride (235 mg, yield 97%) was obtained as a white powder from tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (192 mg, 0.5 mmol) and 1,5-dimethyl-1H-pyrazole-3-carbonyl chloride (118 mg, 0.75 mmol) according to a method similar to the method of Example 223.

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.18-2.25 (1H, m), 2.32 (3H, s), 2.33 (3H, s), 2.53 (2H, brs), 3.73 (3H, s), 3.82 (2H, brs), 6.38 (1H, s), 7.20 (2H, d, J = 7.8 Hz), 7.24 (2H, d, J = 7.8 Hz), 8.31 (3H, s), 9.58 (1H, brs).

Example 406

[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetic acid dihydrochloride

[5-(Aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetic acid dihydrochloride (0.56 g, yield 94%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetic acid (0.63 g, 1.43 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) : 1.03 (9H, s), 2.41 (3H, s), 2.73 (3H, brs), 3.19 (2H, brs), 3.35-3.45 (2H, m), 3.75-3.90 (2H, m), 7.16 (2H, d, J = 7.4 Hz), 7.38 (2H, d, J = 7.4 Hz), 8.16 (3H, brs).

Example 407

(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl [5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetate dihydrochloride

1) (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl [5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetate (0.091 g, yield 28%) was obtained

as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetic acid (0.63 g, 1.43 mmol) according to a method similar to the method of Example 176-1).

^{1}H-NMR ($CDCl_3$) : 1.02 (9H, s), 1.37 (9H, s), 2.14 (3H, s), 2.40 (3H, s), 2.48 (3H, s), 2.83 (2H, s), 3.39 (2H, s), 4.09 (2H, d, J = 4.9 Hz), 4.10-4.25 (1H, m), 4.76 (2H, s), 6.94 (2H, d, J = 7.9 Hz), 7.21 (2H, d, J = 7.9 Hz).

2) (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl [5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetate dihydrochloride (0.085 g, yield 99%) was obtained as a pale-yellow powder from (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl [5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetate (0.090 g, 0.16 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) : 1.01 (9H, s), 2.14 (3H, s), 2.38 (3H, s), 2.71 (3H, brs), 3.13 (2H, brs), 3.52 (2H, brs), 3.73 (2H, brs), 4.92 (2H, s), 7.10 (2H, d, J = 7.5 Hz), 7.31 (2H, d, J = 7.5 Hz), 8.15 (3H, brs).

Example 408

methyl 5-(aminomethyl)-6-isobutyl-2-(methoxymethyl)-4-(4-methylphenyl)nicotinate

1) A mixture of methyl 4-methoxyacetate (5.85 g, 40 mmol), ammonium acetate (15.4 g, 200 mmol), acetic acid (2.3 mL, 40 mmol) and toluene (100 mL) was heated under reflux using a Dean-Stark trap for 10 hrs. The reaction mixture was allowed to cool to room temperature, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give methyl 3-amino-4-methoxybut-2-enoate as a crude product (5.8 g). Methyl 5-cyano-6-isobutyl-2-(methoxymethyl)-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (7.8 g, yield 55%) was obtained as a pale-yellow powder from the crude product (5.8 g), 5-

methyl-3-oxohexanenitrile (5.7 g, purity 87.5%, 40 mmol) and p-tolualdehyde (4.8 g, 40 mmol) according to a method similar to the method of Example 1-2).

^{1}H-NMR ($CDCl_3$) : 0.97 (6H, dd, J = 6.6, 12.8 Hz), 1.80-2.00 (1H, m), 2.20-2.40 (2H, m), 2.31 (3H, s), 3.48 (3H, s), 3.57 (3H, s), 4.56 (1H, s), 4.64 (1H, d, J = 16.4 Hz), 4.73 (1H, d, J = 16.4 Hz), 7.05-7.15 (5H, m).

2) Methyl 5-cyano-6-isobutyl-2-(methoxymethyl)-4-(4-methylphenyl)nicotinate (7.5 g, yield 99%) was obtained as a white powder from methyl 5-cyano-6-isobutyl-2-(methoxymethyl)-4-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (7.7 g, 22 mmol) according to a method similar to the method of Example 23-3).

^{1}H-NMR ($CDCl_3$) : 1.00 (6H, d, J = 6.6 Hz), 2.20-2.35 (1H, m), 2.41 (3H, s), 2.97 (2H, d, J = 7.2 Hz), 3.37 (3H, s), 3.59 (3H, s), 4.71 (2H, s), 7.15-7.35 (4H, m).

3) Methyl 5-(aminomethyl)-6-isobutyl-2-(methoxymethyl)-4-(4-methylphenyl)nicotinate (7.1 g, yield 93%) was obtained as a pale-yellow oil from methyl 5-cyano-6-isobutyl-2-(methoxymethyl)-4-(4-methylphenyl)nicotinate (7.4 g, 21 mmol) according to a method similar to the method of Example 1-4).

^{1}H-NMR ($CDCl_3$) : 0.97 (6H, d, J = 6.8 Hz), 1.22 (2H, brs), 2.15-2.30 (1H, m), 2.39 (3H, s), 2.82 (2H, d, J = 7.4 Hz), 3.36 (3H, s), 3.49 (3H, s), 3.67 (2H, s), 4.65 (2H, s), 7.11 (2H, d, J = 8.1 Hz), 7.21 (2H, d, J = 8.1 Hz).

Example 409

{6-methyl-4-(4-methylphenyl)-2-neopentyl-5-[(pyridin-2-ylthio)methyl]pyridin-3-yl}methylamine trihydrochloride

1) tert-Butyl ({6-methyl-4-(4-methylphenyl)-2-neopentyl-5-[(pyridin-2-ylthio)methyl]pyridin-3-yl}methyl)carbamate (480 mg, yield 78%) was obtained as a powder from [5-({[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl methanesulfonate (600 mg, 1.2 mmol) and 2-mercaptopyridine (145 mg, 1.3 mmol) according to a

method similar to the method of Example 33-1).

^{1}H-NMR ($CDCl_3$) :1.02 (9H, s), 1.37 (9H, s), 2.35 (3H, s), 2.62 (3H, s), 2.83 (2H, s), 4.08 (2H, d, J=4.9 Hz), 4.14 (2H, s), 4.19 (1H, s), 6.91-6.95 (1H, m), 7.03-7.06 (3H, m), 7.17 (2H, d, J=7.91 Hz), 7.39-7.45 (1H, m), 8.31 (1H, d, J=4.1 Hz).

2) (6-Methyl-4-(4-methylphenyl)-2-neopentyl-5-[(pyridin-2-ylthio)methyl]pyridin-3-yl}methylamine trihydrochloride (167 mg, yield 82%) was obtained as a powder from tert-butyl ({6-methyl-4-(4-methylphenyl)-2-neopentyl-5-[(pyridin-2-ylthio)methyl]pyridin-3-yl}methyl)carbamate (200 mg, 0.395 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.03 (9H, s), 2.36 (3H, s), 2.90 (3H, s), 3.28 (2H, s), 3.83 (2H, d, J=4.7 Hz), 4.19 (2H, s), 7.11-7.16 (1H, m), 7.23-7.33 (5H, m), 7.62-7.67 (1H, m), 8.31 (3H, brs), 8.33-8.34 (1H, m).

Example 410

{6-methyl-4-(4-methylphenyl)-2-neopentyl-5-[(1H-1,2,4-triazol-3-ylthio)methyl]pyridin-3-yl}methylamine dihydrochloride

1) tert-Butyl ({6-methyl-4-(4-methylphenyl)-2-neopentyl-5-[(4H-1,2,4-triazol-3-ylthio)methyl]pyridin-3-yl}methyl)carbamate (455 mg, yield 2%) was obtained as a powder from [5-({[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl methanesulfonate (600 mg, 1.2 mmol) and 3-mercapto-1,2,4-triazole (131 mg, 1.3 mmol) according to a method similar to the method of Example 33-1).

^{1}H-NMR ($CDCl_3$) :1.01 (9H, s), 1.37 (9H, s), 2.37 (3H, s), 2.64 (3H, s), 2.83 (2H, s), 4.08 (2H, d, J=4.9 Hz), 4.12 (2H, s), 4.22 (1H, s), 7.04 (2H, d, J=7.7 Hz), 7.20 (2H, d, J=7.7 Hz), 8.02 (1H, s).

2) {6-Methyl-4-(4-methylphenyl)-2-neopentyl-5-[(1H-1,2,4-triazol-3-ylthio)methyl]pyridin-3-yl}methylamine dihydrochloride (160 mg, yield 85%) was obtained as a powder from tert-butyl ({6-methyl-4-(4-methylphenyl)-2-neopentyl-5-

[(4H-1,2,4-triazol-3-ylthio)methyl]pyridin-3-yl}methyl)carbamate (200 mg, 0.403 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.02 (9H, s), 2.39 (3H, s), 2.86 (3H, s), 3.21 (2H, s), 3.81 (2H, d, J=4.1 Hz), 4.08 (2H, s), 7.24 (2H, d, J=8.0 Hz), 7.35 (2H, m, J=8.0 Hz), 8.23 (3H, brs), 8.45 (1H, s).

Example 411

[5-[(1H-imidazol-2-ylthio)methyl]-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methylamine trihydrochloride

1) tert-Butyl {[5-[(1H-imidazol-2-ylthio)methyl]-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (373 mg, yield 75%) was obtained as a powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl methanesulfonate (500 mg, 1.0 mmol) and 2-mercaptoimidazole (110 mg, 1.1 mmol) according to a method similar to the method of Example 33-1).

^{1}H-NMR ($CDCl_3$) :1.01 (9H, s), 1.37 (9H, s), 2.41 (3H, s), 2.55 (3H, s), 2.82 (2H, s), 3.94 (2H, s), 4.06 (2H, d, J=4.9 Hz), 4.20 (1H, s), 6.94 (1H, brs), 7.01 (2H, d, J=7.9 Hz), 7.06 (1H, brs), 7.23 (2H, d, J=7.9 Hz).

2) [5-[(1H-Imidazol-2-ylthio)methyl]-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methylamine trihydrochloride (160 mg, yield 79%) was obtained as a powder from tert-butyl {[5-[(1H-imidazol-2-ylthio)methyl]-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (200 mg, 0.404 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.01 (9H, s), 2.40 (3H, s), 2.67 (3H, s), 3.07 (2H, brs), 3.74 (2H, brs), 4.17 (2H, s), 7.18 (2H, d, J=7.9 Hz), 7.33 (2H, d, J=7.9 Hz), 7.70 (2H, s), 8.26 (3H, brs).

Example 412

{6-methyl-4-(4-methylphenyl)-2-neopentyl-5-[(pyrimidin-2-

ylthio)methyl]pyridin-3-yl}methylamine trihydrochloride

1) tert-Butyl ({6-methyl-4-(4-methylphenyl)-2-neopentyl-5-[(pyrimidin-2-ylthio)methyl]pyridin-3-yl}methyl)carbamate (380 mg, yield 77%) was obtained as a powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl methanesulfonate (500 mg, 1.0 mmol) and 2-mercaptopyrimidine (123 mg, 1.1 mmol) according to a method similar to the method of Example 33-1).

^{1}H-NMR ($CDCl_3$) :1.02 (9H, s), 1.37 (9H, s), 2.35 (3H, s), 2.65 (3H, s), 2.83 (2H, s), 4.08 (2H, d, J=4.9 Hz), 4.14 (2H, s), 4.19 (1H, brs), 6.92 (1H, t, J=4.9 Hz), 7.06 (2H, d, J=7.8 Hz), 7.18 (2H, d, J=7.8 Hz), 8.43 (2H, d, J=4.9 Hz).

2) (6-Methyl-4-(4-methylphenyl)-2-neopentyl-5-[(pyrimidin-2-ylthio)methyl]pyridin-3-yl}methylamine trihydrochloride (180 mg, yield 88%) was obtained as a powder from tert-butyl ({6-methyl-4-(4-methylphenyl)-2-neopentyl-5-[(pyrimidin-2-ylthio)methyl]pyridin-3-yl}methyl)carbamate (200 mg, 0.395 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.02 (9H, s), 2.35 (3H, s), 2.85 (3H, s), 3.17 (2H, brs), 3.80 (2H, s), 4.18 (2H, s), 7.21-7.13 (5H, m), 8.22 (3H, brs), 8.57 (2H, d, J=4.9 Hz).

Example 413

[5-{[(5-methoxy-1H-benzimidazol-2-yl)thio]methyl}-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methylamine trihydrochloride

1) tert-Butyl ([5-{[(5-methoxy-1H-benzimidazol-2-yl)thio]methyl}-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (530 mg, yield 92%) was obtained as a powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl methanesulfonate (500 mg, 1.0 mmol) and 5-methoxy-2-benzimidazolethiol (198 mg, 1.1 mmol) according to a method similar to the method of Example 33-1).

^{1}H-NMR ($CDCl_3$) :1.02 (9H, s), 1.37 (9H, s), 2.33 (3H, s), 2.64 (3H, s), 2.83 (2H, s), 3.82 (3H, s), 4.07 (2H, d, J=5.1 Hz), 4.22 (2H, s), 4.25 (1H, s), 6.77-6.84 (2H, m), 7.01 (2H, d, J=7.9 Hz), 7.14-7.16 (3H, m), 7.49 (1H, d, J=8.9 Hz).

2) [5-{[(5-Methoxy-1H-benzimidazol-2-yl)thio]methyl}-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methylamine trihydrochloride (194 mg, yield 91%) was obtained as a powder from tert-butyl {[5-{[(5-methoxy-1H-benzimidazol-2-yl)thio]methyl}-6-methyl-4-(4-methylphenyl)-2-neopentylpyridin-3-yl]methyl}carbamate (200 mg, 0.365 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.02 (9H, s), 2.30 (3H, s), 2.83 (3H, s), 3.12 (2H, brs), 3.77 (2H, s), 3.81 (3H, s), 4.37 (2H, s), 6.94-7.02 (2H, m), 7.20-7.27 (4H, m), 7.46 (1H, d, J=8.9 Hz), 8.23 (3H, brs).

Example 414

methyl 3-{[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1H-pyrazole-5-carboxylate dihydrochloride

1) Methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1H-pyrazole-5-carboxylate (800 mg, yield 52%) was obtained as a powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methyl methanesulfonate (1.4 g, 2.85 mmol) and methyl 3-hydroxy-1H-pyrazole-5-carboxylate (426 mg, 3.0 mmol) according to a method similar to the method of Example 33-1).

^{1}H-NMR ($CDCl_3$) :1.02 (9H, s), 1.37 (9H, s), 2.36 (3H, s), 2.62 (3H, s), 2.86 (2H, s), 3.89 (3H, s), 4.13 (2H, d, J=4.5 Hz), 4.20 (1H, brs), 4.84 (2H, s), 6.13 (1H, s), 7.04 (2H, d, J=7.8 Hz), 7.16 (2H, d, J=7.8 Hz), 9.89 (1H, brs).

2) Methyl 3-{[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1H-pyrazole-5-carboxylate dihydrochloride (142 mg, yield 75%) was obtained as a powder

from methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1H-pyrazole-5-carboxylate (200 mg, 0.373 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.03 (9H, s), 2.37 (3H, s), 2.84 (3H, s), 3.23 (2H, brs), 3.81 (3H, s), 3.87 (2H, brs), 4.83 (2H, s), 6.17 (1H, s), 7.25 (2H, d, J=7.9 Hz), 7.33 (1H, d, J=7.9 Hz), 8.29 (3H, brs).

Example 415

3-{[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1H-pyrazole-5-carboxylic acid dihydrochloride

1) 3-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1H-pyrazole-5-carboxylic acid (914 mg, yield 81%) was obtained as a white solid from methyl 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1H-pyrazole-5-carboxylate (1:16 g, 2.16 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR (DMSO-d_6) :1.00 (9H, s), 1.34 (9H, s), 2.32 (3H, s), 2.53 (3H, s), 2.69 (2H, s), 3.87 (2H, d, J=3.2 Hz), 4.73 (2H, s), 6.06 (1H, s), 6.83 (1H, t, J=4.1 Hz), 7.13-7.21 (4H, m), 12.91 (1H, s).

2) 3-{[5-(Aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1H-pyrazole-5-carboxylic acid dihydrochloride (180 mg, yield 95%) was obtained as a white powder from 3-{[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]methoxy}-1H-pyrazole-5-carboxylic acid (200 mg, 0.383 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.03 (9H, s), 2.37 (3H, s), 2.51 (3H, s), 2.78 (2H, s), 3.85 (2H; s), 4.80 (2H, s), 6.09 (1H, s), 7.23 (2H, d, J=7.9 Hz), 7.32 (2H, d, J=7.9 Hz), 8.16 (3H, brs).

Example 416

4-(methoxycarbonyl)benzyl 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate dihydrochloride

1) 4-(Methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate (7.36 g, yield 70%) was obtained as a white solid from 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid (7.8 g, 18.3 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :1.01 (9H, s), 1.36 (9H, s), 2.35 (3H, s), 2.53 (3H, s), 2.87 (2H, s), 3.93 (3H, s), 4.17 (2H, s), 4.98 (2H, s), 7.02 (2H, d, J=7.9 Hz), 7.09 (2H, d, J=8.2 Hz), 7.11 (2H, d, J=7.9 Hz), 7.93 (2H, d, J=8.2 Hz).

2) 4-(Methoxycarbonyl)benzyl 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate dihydrochloride (181 mg, yield 95%) was obtained as a white powder from 4-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate (200 mg, 0.348 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (9H, s), 2.33 (3H, s), 2.51 (3H, s), 2.90 (2H, s), 3.83 (2H, s), 3.86 (3H, s), 5.07 (2H, s), 7.12-7.21 (6H, m), 7.87 (2H, d, J=8.3 Hz), 8.13 (3H, brs).

Example 417

4-[({[5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]carbonyl}oxy)methyl]benzoic acid dihydrochloride

1) 4-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]carbonyl}oxy)methyl]benzoic acid (1.68 g, yield 86%) was obtained as a white solid from 4-(methoxycarbonyl)benzyl 5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinate (2.0 g, 3.48 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :1.01 (9H, s), 1.37 (9H, s), 2.35 (3H, s), 2.55

(3H, s), 2.89 (2H, s), 4.16-4.20 (3H, m), 5.01 (2H, s), 7.02-7.13 (6H, m), 7.99 (2H, d, J=8.3 Hz).

2) 4-[({[5-(Aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]carbonyl}oxy)methyl]benzoic acid dihydrochloride (150 mg, yield 79%) was obtained as a white powder from 4-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-2-methyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]carbonyl}oxy)methyl]benzoic acid (200 mg, 0.357 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (9H, s), 2.34 (3H, s), 2.51 (3H, s), 2.90 (2H, s), 3.84 (2H, d, J=5.7 Hz), 5.06 (2H, s), 7.10-7.18 (6H, m), 7.85 (2H, d, J=8.3 Hz), 8.11 (3H, brs).

Example 418

4-(trifluoromethyl)benzyl [5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate dihydrochloride

1) 4-(Trifluoromethyl)benzyl [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate (350 mg, yield 85%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (300 mg, 0.703 mmol) and 1-(bromomethyl)-4-(trifluoromethyl)benzene (250 mg, 1.05 mmol) according to a method similar to the method of Example 169-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.8 Hz), 1.37 (9H, s), 2.11-2.29 (1H, m), 2.37 (3H, s), 2.48 (3H, s), 2.75 (2H, d, J = 6.6 Hz), 3.42 (2H, s), 4.03 (2H, d, J = 5.1 Hz), 4.20 (1H, brs), 5.09 (2H, s), 6.91 (2H, d, J = 7.7 Hz), 7.14 (2H, d, J = 7.7 Hz), 7.33 (2H, d, J = 8.1 Hz), 7.60 (2H, d, J = 8.1 Hz).

2) 4-(Trifluoromethyl)benzyl [5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate dihydrochloride (283 mg, yield 66%) was obtained as a white powder from 4-(trifluoromethyl)benzyl [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate (330 mg, 0.564 mmol)

according to a method similar to the method of Example 2-3).
^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 2.09-2.25 (1H, m), 2.36 (3H, s), 2.77 (3H, s), 3.12 (2H,s), 3.77 (2H, d, J = 5.1 Hz), 5.14 (2H, s), 7.09 (2H, d, J = 8.1 Hz), 7.24 (2H, d, J = 8.1Hz), 7.47 (2H, d, J = 8.1 Hz), 7.76 (2H, d, J = 8.1 Hz), 8.35 (3H, brs).

Example 419

4-fluorobenzyl [5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate dihydrochloride

1) 4-Fluorobenzyl [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate (325 mg, yield 86%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (300 mg, 0.703 mmol) and 1-(bromomethyl)-4-fluorobenzene (198 mg, 1.05 mmol) according t a method similar to the method of Example 169-1).
^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.11-2.26 (1H, m), 2.38 (3H, s), 2.46 (3H, s), 2.74 (2H, d, J = 7.4 Hz), 3.38 (2H, s), 4.02 (2H, d, J = 4.9 Hz), 4.20 (1H, brs), 5.00 (2H, s), 6.90 (2H, d, J = 7.9 Hz), 6.88-7.07 (2H, m),7.14 (2H, d, J = 7.9 Hz), 7.15-7.25 (2H, m).

2) 4-Fluorobenzyl [5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate dihydrochloride (234 mg, yield 82%) was obtained as a white powder from 4-fluorobenzyl [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetate (300 mg, 0.561 mmol) according to a method similar to the method of Example 2-3).
^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.12-2.26 (1H, m), 2.38 (3H, s), 2.84 (3H, s), 3.26 (2H, d, J = 6.8 Hz), 3.79 (2H, d, J = 4.5 Hz), 5.03 (2H, s), 7.12 (2H, d, J = 7.9 Hz), 7.17-7.39 (6H, m), 8.57 (3H, brs).

Example 420

{[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(2-oxo-2-pyrrolidin-1-ylethyl)pyridin-3-yl]methyl}amine dihydrochloride

1) tert-Butyl {[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(2-oxo-2-pyrrolidin-1-ylethyl)pyridin-3-yl]methyl}carbamate (120 mg, yield 36%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (300 mg, 0.703 mmol) and pyrrolidine (440 mg, 2.11 mmol) according to a method similar to the method of Example 311-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.37 (9H, s), 2.12-2.25 (1H, m), 2.39 (3H, s), 2.55 (3H, s), 2.74 (2H, d, J = 7.4 Hz), 2.86-2.97 (4H, m), 3.28 (2H, s), 3.36 (2H, t, J = 6.5 Hz), 4.03 (2H, d, J = 4.7 Hz), 4.20 (1H, brs), 7.01 (2H, d, J = 7.9 Hz), 7.21 (2H, d, J = 7.9 Hz).

2) {[2-Isobutyl-6-methyl-4-(4-methylphenyl)-5-(2-oxo-2-pyrrolidin-1-ylethyl)pyridin-3-yl]methyl}amine dihydrochloride (62.4 mg, yield 56%) was obtained as a white powder from tert-butyl {[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(2-oxo-2-pyrrolidin-1-ylethyl)pyridin-3-yl]methyl}carbamate (100 mg, 0.208 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.11-2.26 (1H, m), 2.40 (3H, s), 2.80 (3H, s), 2.88 (2H, t, J = 6.1 Hz), 3.12-3.29 (4H, m), 3.42 (2H, s), 3.81 (2H, s), 7.17 (2H, d, J = 7.9 Hz), 7.38 (2H, d, J = 7.9 Hz), 8.43 (3H, brs).

Example 421

ethyl 1-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}piperidine-4-carboxylate dihydrochloride

1) Ethyl 1-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}piperidine-4-carboxylate (330 mg, yield 50%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (500 mg, 1.17 mmol) and ethyl piperidine-4-carboxylate (553 mg, 3.52 mmol) according to a method similar to the method of Example 311-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.27 (3H, t, J = 7.2 Hz), 1.37 (9H, s), 1.54 (1H, dd, J = 13.2, 9.8 Hz), 1.64-1.75 (1H, m), 1.87 (1H, dd, J = 13.2, 2,6 Hz), 2.12-2.27 (1H, m), 2.38 (3H, s), 2.49 (3H, s), 2.74 (2H, d, J = 7.2 Hz), 2.81-3.01 (3H, m), 3.30 (2H, s), 3.49-3.60 (1H, m), 4.15 (2H, q, J = 7.2 Hz), 4.20 (1H, brs), 6.98 (2H, d, J = 8.1 Hz), 7.21 (2H, d, J = 8.1 Hz).

2) Ethyl 1-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}piperidine-4-carboxylate dihydrochloride (8.2 mg, yield 43%) was obtained as a white powder from ethyl 1-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}piperidine-4-carboxylate (20 mg, 0.0354 mmol) according to a method similar to the method of Example 2-3).
EIMS(M+1):466.

Example 422

1-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}piperidine-4-carboxylic acid dihydrochloride

1) 1-{[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}piperidine-4-carboxylic acid (240 mg, yield 87%) was obtained as a white powder from ethyl 1-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}piperidine-4-carboxylate (290 mg, 0.513 mmol) according to a method similar to the method of Example 9-1).
^{1}H-NMR ($CDCl_3$) :1.01 (6H, d, J = 6.4 Hz), 1.37 (9H, s), 1.48-1.62 (1H, m), 1.73 (1H, d, J = 11.1 Hz), 1.89 (1H, d, J = 10.6 Hz), 2.14-2.29 (1H, m), 2.40 (3H, s), 2.74 (3H, s), 2.77-3.00 (2H, m), 3.06 (2H, d, J = 6.0 Hz), 3.42 (2H, s), 3.53 (1H, d, J = 12.8 Hz), 4.10 (2H, d, J = 5.09 Hz), 4.20 (1H, brs), 4.26 (1H, d, J = 12.6 Hz), 4.65 (1H, s), 7.01 (2H, d, J = 7.5 Hz), 7.27 (2H, d, J = 7.5 Hz).

2) 1-{[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}piperidine-4-carboxylic acid dihydrochloride (220 mg, yield 100%) was obtained as a white

powder from 1-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}piperidine-4-carboxylic acid (230 mg, 0.428 mmol) according to a method similar to the method of Example 2-3).

EIMS(M+1):438

Example 423

N-2-adamantyl-2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetamide dihydrochloride

1) tert-Butyl {[5-[2-(2-adamantylamino)-2-oxoethyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (50 mg, yield 13%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (300 mg, 0.703 mmol) and 2-adamantanamine (396 mg, 2.11 mmol) according to a method similar to the method of Example 311-1).

^{1}H-NMR ($CDCl_3$) :0.95 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 1.53-1.63 (2H, m), 1.67-1.84 (9H, m), 2.12-2.26 (1H, m), 2.39 (3H, s), 2.57 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.30 (2H, s), 3.97 (2H, d, J = 8.1 Hz), 4.06 (2H, d, J = 5.09 Hz), 4.20 (1H, brs), 4.22 (1H, s), 5.45 (1H, d, J = 8.3 Hz), 6.96 (2H, d, J = 7.9 Hz), 7.22 (2H, d, J = 7.9 Hz).

2) N-2-Adamantyl-2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetamide dihydrochloride (45.1 mg, yield 100%) was obtained as a white powder from tert-butyl {[5-[2-(2-adamantylamino)-2-oxoethyl]-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (48 mg, 0.0857 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.4 Hz), 1.47 (2H, d, J = 12.1 Hz), 1.63-1.94 (12H, m), 2.08-2.26 (1H, m), 2.40 (3H, s), 2.80 (3H, s), 3.22 (2H, d, J = 5.84 Hz), 3.44 (2H, s), 3.81 (2H, s), 7.19 (2H, d, J = 7.9 Hz), 7.34 (2H, d, J = 7.9 Hz), 7.87 (1H, d, J = 7.7 Hz), 8.49 (3H, brs).

Example 424

2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-

methylphenyl)pyridin-3-yl]-N-(2-thienylmethyl)acetamide dihydrochloride

1) [5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (500 mg, 1.17 mmol) and thiophene-2-methylamine (133 mg, 1.17 mmol) were dissolved in tetrahydrofuran (5 mL) and diethyl cyanophosphonate (286 mg, 1.75 mmol) was added under ice-cooling. The obtained reacti n mixture was stirred at room temperature for 16 hrs. The reaction mixture was poured into saturated brine, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give tert-butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{2-oxo-2-[(2-thienylmethyl)amino]ethyl}pyridin-3-yl)methyl]carbamate (493 mg, yield 81 %) as a white powder.

^{1}H-NMR ($CDCl_3$) :0.96 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.11-2.27 (1H, m), 2.37 (3H, s), 2.56 (3H, s), 2.76 (2H, d, J = 7.2 Hz), 3.30 (2H, s), 4.03 (2H, d, J = 4.9 Hz), 4.20 (1H, brs), 4.51 (2H, d, J = 5.7 Hz), 6.85-7.00 (4H, m), 7.16 (2H, d, J = 7.9 Hz), 7.23 (1H, dd, J = 5.1, 1,1 Hz).

2) 2-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N-(2-thienylmethyl)acetamide dihydrochloride (300 mg, yield 66%) was obtained as a white powder from tert-butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{2-oxo-2-[(2-thienylmethyl)amino]ethyl}pyridin-3-yl)methyl]carbamate (480 mg, 0.92 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.6 Hz), 2.12-2.33 (1H, m), 2.37 (3H, s), 2.47 (3H, s), 2.59 (2H, s), 3.28 (2H, s), 3.76 (2H, s), 4.37 (2H, d, J = 5.8 Hz), 6.89-6.94 (1H, m), 6.97 (1H, dd, J = 5.0, 3.5 Hz), 7.43 (1H, dd, J = 5.0, 1.2 Hz), 8.04 (3H, brs).

Exampl 425

2-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N-(pyridin-3-ylmethyl)acetamide trihydrochloride

1) tert-Butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{2-oxo-2-[(pyridin-3-ylmethyl)amino]ethyl}pyridin-3-yl)methyl]carbamate (394 mg, yield 65%) was obtained as a white powder from [5-({[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (500 mg, 1.17 mmol) and 3-(aminomethyl)pyridine (133 mg, 1.17 mmol) according to a method similar to the method of Example 424-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.37 (9H, s), 2.14-2.29 (1H, m), 2.38 (3H, s), 2.55 (3H, s), 2.75 (2H, d, J = 7.2 Hz), 4.02 (2H, d, J = 4.9 Hz), 4.20 (1H, brs), 4.35 (2H, d, J = 5.8 Hz), 5.47 (1H, s), 6.88 (2H, d, J = 7.9 Hz), 7.15 (2H, d, J = 7.7 Hz), 7.54 (1H, d, J = 7.7 Hz), 8.45 (1H, d, J = 1.5 Hz), 8.55 (1H, dd, J = 4.7, 1.3 Hz).

2) 2-[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-N-(pyridin-3-ylmethyl)acetamide trihydrochloride (380 mg, yield 98%) was obtained as a white powder from tert-butyl [(2-isobutyl-6-methyl-4-(4-methylphenyl)-5-{2-oxo-2-[(pyridin-3-ylmethyl)amino]ethyl}pyridin-3-yl)methyl]carbamate (380 mg, 0.74 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.11-2.24 (1H, m), 2.40 (3H, s), 2.78 (3H, s), 3.20 (2H, d, J = 7.4 Hz), 3.43 (2H, s), 4.37 (2H, d, J = 5.7 Hz), 7.16 (2H, d, J = 8.1 Hz), 7.33 (2H, d, J = 8.1 Hz), 8.00 (1H, dd, J = 8.0, 5.6 Hz), 8.28 (1H, d, J = 8.1 Hz), 8.48 (3H, brs), 8.70-8.77 (1H, m), 8.80-8.85 (1H, m).

Example 426

methyl 4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)thiophene-3-carboxylate dihydrochloride

1) [5-({[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (500 mg, 1.17 mmol),

methyl 4-aminothiophene-3-carboxylate (184 mg, 1.17 mmol) and O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluromium hexafluorophosphate (HATU, 1.0 g, 1.75 mmol) were dissolved in N,N-dimethylformamide (10 mL) and the mixture was stirred at room temperature for 24 hrs. The reaction mixture was poured into saturated brine, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give methyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)thiophene-3-carboxylate (440 mg, yield 66%) as a white powder.

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.4 Hz), 1.40 (9H, s), 2.24-2.33 (1H, m), 2.35 (3H, s), 2.53 (3H, s), 2.77 (2H, d, J = 7.2 Hz), 3.52 (2H, s), 3.79 (3H, s), 4.06 (2H, d, J = 4.1 Hz), 4.20 (1H, brs), 7.02 (2H, d, J = 7.9 Hz), 7.17 (2H, d, J = 7.9 Hz), 7.95-7.98 (1H, m), 7.98-8.02 (1H, m).

2) Methyl 4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)thiophene-3-carboxylate dihydrochloride (161 mg, yield 65%) was obtained as a white powder from methyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)thiophene-3-carboxylate (262 mg, 0.46 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.6 Hz), 2.11-2.27 (1H, m), 2.35 (3H, s), 2.48 (3H, s), 2.80 (2H, s), 3.14 (2H, s), 3.76-3.86 (5H, m), 7.17 (2H, d, J = 7.9 Hz), 7.32 (2H, d, J = 7.9 Hz), 7.80 (1H, d, J = 3.2 Hz), 8.26-8.45 (3H brs), 9.69 (s, 1H).

Example 427

4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)thiophene-3-carboxylic

acid dihydrochloride

1) 4-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)thiophene-3-carboxylic acid (183 mg, yield 67%) was obtained as a white powder from methyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)thiophene-3-carboxylate (280 mg, 0.495 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.40 (9H, s), 2.11-2.24 (1H, m), 2.36 (3H, s), 2.52 (3H, s), 2.78 (2H, s), 3.49 (2H, s), 4.03 (2H, s), 4.20 (1H, brs), 6.98-7.25 (4H, m), 7.85-8.05 (2H, m).

2) 4-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)thiophene-3-carboxylic acid dihydrochloride (143 mg, yield 64%) was obtained as a white powder from 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)thiophene-3-carboxylic acid (170 mg, 0.428 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.11-2.27 (1H, m), 2.35 (3H, s), 2.50 (3H, s), 2.79 (2H, s), 3.14 (2H, s), 3.81 (2H, s), 7.17 (2H, d, J = 8.1 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.79 (1H, d, J = 3.6 Hz), 8.29 (1H, d, J = 3.6 Hz), 8.33-8.44 (3H, s), 9.89 (1H, s).

Example 428

methyl 4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoate dihydrochloride

1) Methyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoate (442 mg, yield 67%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (500 mg, 1.17 mmol) and methyl 4-aminobenzoate (177 mg, 1.17 mmol) according to a method similar to the method of Example

426-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.15-2.28 (1H, m), 2.63 (3H, s), 2.77 (2H, d, J = 7.4 Hz), 3.47 (2H, s), 3.89 (3H, s), 4.06 (2H, d, J = 5.1 Hz), 4.20 (1H, brs), 7.01 (2H, d, J = 7.9 Hz), 7.23 (2H, d, J = 7.9 Hz), 7.42 (2H, d, J = 8.7 Hz), 7.97 (2H, d, J = 8.7 Hz).

2) Methyl 4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoate dihydrochloride (142 mg, yield 97%) was obtained as a white powder from methyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoate (154 mg, 0.275 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.10-2.30 (1H, m), 2.36 (3H, s), 2.49 (3H, s), 2.71 (2H, s), 3.01 (2H, s), 3.77 (2H, s), 3.82 (3H, s), 7.17 (2H, d, J = 8.1 Hz), 7.32 (2H, d, J = 8.1 Hz), 7.62 (2H, d, J = 8.9 Hz), 7.90 (2H, d, J = 8.9 Hz), 8.15 (3H, brs).

Example 429

4-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoic acid dihydrochloride

1) 4-({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoic acid (275 mg, yield 100%) was obtained as a white powder from methyl 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoate (280 mg, 0.500 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) :0.99 (6H, d, J = 6.2 Hz), 1.37 (9H, s), 2.12-2.27 (1H, m), 2.35 (3H, s), 2.87 (3H, s), 3.19 (2H, s), 3.87 (2H, s), 4.15 (2H, d, J = 6.2 Hz), 4.20 (1H, brs), 7.10 (2H, d, J = 8.1 Hz), 7.25 (2H, d, J = 8.1 Hz), 7.68 (2H, d, J = 8.5 Hz), 8.68 (2H, d, J = 8.5 Hz).

2) 4-({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoic acid

dihydrochloride (235 mg, yield 92%) was obtained as a white powder from 4-({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoic acid (270 mg, 0.495 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :1.00 (6H, d, J = 6.6 Hz), 2.12-2.28 (1H, m), 2.37 (3H, s), 2.50 (3H, s), 2.80 (2H, s), 3.15 (2H, s), 3.82 (2H, s), 7.20 (2H, d, J = 8.1 Hz), 7.34 (2H, d, J = 8.1 Hz), 7.60 (2H, d, J = 8.9 Hz), 7.87 (2H, d, J = 8.9 Hz), 8.35 (3H, brs).

Example 430

ethyl 2-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]-1,3-thiazole-4-carboxylate dihydrochloride

1) Ethyl 2-({[(benzyloxy)carbonyl]amino}methyl)-1,3-thiazole-4-carboxylate (3.5 g, 10.9 mmol) was dissolved in 30% hydrogen bromide acetic acid solution (50 mL), and the solution was stirred at room temperature for 2 hrs. White precipitate was collected by filtration and dissolved in saturated aqueous sodium hydrogen carbonate. The obtained solution was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate. The insoluble material was filtered off and the filtrate was concentrated under reduced pressure to give ethyl 2-(aminomethyl)-1,3-thiazole-4-carboxylate (793 mg, yield 40%) as an oil. Ethyl 2-[({[5-({[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]-1,3-thiazole-4-carboxylate (649 mg, yield 100%) was obtained as a white powder from the oil (793 mg) and [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (454 mg, 1.07 mmol) according to a method similar to the method of Example 424-1).

^{1}H-NMR ($CDCl_3$) :0.97 (6H, d, J = 6.6 Hz), 1.35-1.47 (12H, m), 2.13-2.28 (1H, m), 2.36 (3H, s), 2.53 (3H, s), 2.75 (2H, d, J = 7.2 Hz), 3.34 (2H, s), 4.03 (2H, d, J = 5.3 Hz), 4.20 (1H, brs), 4.43 (2H, q, J = 7.2

Hz), 4.66 (2H, d, J = 6.0 Hz), 6.93 (2H, d, J = 7.9 Hz), 7.14 (2H, d, J = 7.9 Hz), 8.14 (1H, s).

2) Ethyl 2-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]-1,3-thiazole-4-carboxylate dihydrochloride (138 mg, yield 81%) was obtained as a white powder from ethyl 2-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]-1,3-thiazole-4-carboxylate (178 mg, 0.299 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.98 (6H, d, J = 6.4 Hz), 1.31 (3H, t, J = 7.2 Hz), 2.10-2.23 (1H, m), 2.38 (3H, s), 2.49 (3H, s), 2.77 (2H, s), 3.14 (2H, s), 3.41 (2H, s), 3.80 (2H, s), 4.31 (2H, q, J = 7.2 Hz), 4.51 (2H, d, J = 5.8 Hz), 7.17 (2H, d, J = 8.1 Hz), 7.32 (2H, d, J = 8.1 Hz), 8.36 (3H, brs), 8.91 (1H, s).

Example 431

2-[({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]-1,3-thiazole-4-carboxylic acid dihydrochloride

1) 2-[({[5-{[(tert-Butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]-1,3-thiazole-4-carboxylic acid (438 mg, yield 100%) was obtained as a white powder from ethyl 2-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]-1,3-thiazole-4-carboxylate (460 mg, 0.773 mmol) according to a method similar to the method of Example 9-1).

^{1}H-NMR ($CDCl_3$) : 0.93 (6H, d, J = 6.6 Hz), 1.34 (9H, s), 2.09-2.26 (1H, m), 2.34 (3H, s), 2.40 (2H, s), 2.48 (3H, s), 3.24 (2H, s), 3.80 (2H, s), 4.20 (1H, brs), 4.48 (2H, d, J = 5.8 Hz), 7.09 (2H, d, J = 7.0 Hz), 7.19 (2H, d, J = 7.0 Hz), 8.39 (1H, s).

2) 2-[({[5-(Aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]-1,3-thiazole-4-carboxylic acid dihydrochloride (235 mg, yield 91%) was

obtained as a white powder from 2-[({[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)methyl]-1,3-thiazole-4-carboxylic acid (270 mg, 0.495 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) : 1.00 (6H, d, J = 6.6 Hz), 2.12-2.28 (1H, m), 2.37 (3H, s), 2.50 (3H, s), 2.80 (2H, s), 3.15 (2H, s), 3.82 (2H, s), 7.20 (2H, d, J = 8.1 Hz), 7.34 (2H, d, J = 8.1 Hz), 7.60 (2H, d, J = 8.9 Hz), 7.87 (2H, d, J = 8.9 Hz), 8.35 (3H, brs).

Example 432

methyl 1-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}prolinate dihydrochloride

1) Methyl 1-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}prolinate (456 mg, yield 72%) was obtained as a white powder from [5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid (500 mg, 1.17 mmol) and methyl proline monohydrochloride (194 mg, 1.17 mmol) according to a method similar to the method of Example 426-1).

^{1}H-NMR ($CDCl_3$) :0.98 (6H, d, J = 6.6 Hz), 1.37 (9H, s), 1.84-2.00 (3H, m), 2.05 (3H, s), 2.08-2.24 (2H, m), 2.75 (3H, s), 3.15-3.26 (2H, m), 3.48 (2H, s), 3.71 (3H, s), 4.11-4.21 (3H, m), 4.31-4.55 (2H, m), 7.02-7.15 (2H, m), 7.28-7.41 (2H, m).

2) Methyl 1-{[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}prolinate dihydrochloride (277.5 mg, yield 64%) was obtained as a white powder from methyl 1-{[5-{[(tert-butoxycarbonyl)amino]methyl}-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}prolinate (456 mg, 0.848 mmol) according to a method similar to the method of Example 2-3).

^{1}H-NMR (DMSO-d_6) :0.97 (6H, d, J = 6.4 Hz), 1.76-1.91 (3H, m), 2.04-2.24 (2H, m), 2.40 (3H, s), 2.65 (3H, s), 2.96 (2H, s), 3.17 (2H, t, J = 6.7 Hz), 3.42 (2H, s), 3.61 (3H, s), 3.77 (2H,

s), 4.19-4.32 (2H, m), 7.15 (2H, d, J = 7.4 Hz), 7.37 (2H, d, J = 7.4 Hz), 8.10 (3H, s).

Example 433

N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)benzamide dihydrochloride

To a solution of tert-butyl {[5-amino-2-isobutyl-6-methyl-4-(4-methylphenyl)pyridin-3-yl]methyl}carbamate (383 mg, 1.0 mmol) in tetrahydrofuran (5 mL) was added 3-cyanobenzoyl chloride (245 mg, 1.5 mmol) and triethylamine (280 L, 2.0 mmol) was added. The mixture was stirred for 18 hrs. Saturated aqueous sodium hydrogen carbonate solution (5 mL) 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. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give an oil. To a solution of the obtained oil in ethanol (5 mL) was added hydoxylamine hydrochloride (192 mg, 3.0 mmol) and sodium carbonate (420 mg, 4.0 mmol) and the mixture was stirred at 80 C for 15 hrs. Distilled water (10 mL) 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. The solvent was evaporated under reduced pressure to give an oil. To a solution of the obtained oil in tetrahydrofuran (3 mL) was added N,N'-carbonyldiimidazole (324 mg, 2.0 mmol) and the mixture was stirred at 65 C for 2 hrs. Saturated aqueous sodium carbonate solution (5 mL) 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. Th solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give an oil.

To a solution of the obtained oil in ethyl acetate (2 mL) was added 4N hydrogen chloride ethyl acetate s lution (2 mL) and the mixture was stirred at room temperature for 3 hrs. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from hexane to give N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)benzamide dihydrochloride (115 mg, yield 21%) as a white powder.
^{1}H-NMR (DOSO-d_6) :0.99 (6H, d, J = 6.6 Hz), 2.21-2.29 (1H, m), 2.29 (3H, s), 2.50 (3H, s), 2.96 (2H, s), 3.82 (2H, s), 7.21 (4H, s), 7.62 (1H, t, J = 7.5 Hz), 7.79 (1H, d, J = 7.5 Hz), 7.93 (1H, d, J = 7.5 Hz), 8.25 (3H, brs), 10.13 (1H, brs), 13.12 (1H, brs).

Experimental Example 1

Determination of dipeptidyl peptidase IV inhibitory activity in rat plasma

The reaction was carried out according to the method of Raymond et al. (Diabetes, vol. 47, pp. 1253-1258, 1998) using a 96 well flat-bottomed plate at 30 C. An N,N-dimethylformamide solution (1 L) containing the test compound was added to a mixture of water (69 L), 1 M Tris-hydrochloride buffer (10 L, pH 7.5) and 1 mM aqueous Gly-Pro-p-NA solution (100 L) to prepare a mixed solution. Plasma (20 L) prepared from blood of SD rat by a conventional method was added to the above-mentioned mixed solution and the enzyme reaction was started at 30 C. The absorbance after 0 hr. and 1 hr. was measured using a microplate reader at a wavelength of 405 nm and an increase (ODs) was determined. At the same time, an increase (ODc) in absorbance of the reaction mixture without the test compound, and an increase (ODb) in absorbance of the reaction mixture without the test compound and the enzyme were determined and percent inhibition of dipeptidyl peptidase IV enzyme activity was calculated from the following formula:

{1-[(ODs- ODb)/(ODc- ODb)]}×100

The dipeptidyl peptidase IV inhibitory activity of the test compound group is expressed in IC_{50} value (nM) and shown in Table 5.

Table 5

Test compound (Example No.)	IC_{50} value (nM)
1	520

As shown above, the compound of the present invention has a superior dipeptidyl peptidase IV inhibitory activity, and is useful as an agent for the prophylaxis or treatment of diabetes and the like.

Experimental Example 2

Determination of dipeptidyl peptidase IV inhibitory activity in rat plasma

In the same manner as in Experimental Example 1, the dipeptidyl peptidase IV inhibitory activity of the test compound was determined. The results are shown in Table 6.

Table 6

Test compound (Example No.)	IC_{50} value (nM)
13	25
22	12
26	5.1
40	56
170	100
210	12
267	7.4
305	3.5
312	20
336	19
350	15
421	16
422	7.3

As mentioned above, the compound of the present invention has a superior dipeptidyl peptidase IV inhibitory activity, and therefore, is useful as an agent for the prophylaxis or treatment of diabetes and the like.

Formulation Example 1 (production of capsules)

1) compound of Example 1	30 mg
2) fine cellulose powder	10 mg
3) lactose	19 mg
4) magnesium stearate	1 mg
total	60 mg

1), 2), 3) and 4) are mixed and filled in gelatin capsules.

Formulation Example 2 (production of tablets)

1) compound of Example 1	30 g
2) lactose	50 g
3) corn starch	15 g
4) carboxymethylcellulose calcium	44 g
5) magnesium stearate	1 g
total of 1000 tablets	140 g

The entire amounts of 1), 2) and 3), and 30 g of 4) are kneaded with water, dried in vacuo and granulated. The granules are mixed with 14 g of 4) and 1 g of 5) and the mixture is compressed with a tableting machine, whereby 1000 tablets containing 30 mg of compound of Example 1 per tablet are obtained.

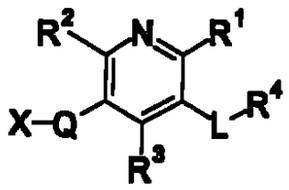
Industrial Applicability

The compound of the present invention shows a superior peptidase-inhibitory activity and is useful as an agent for the prophylaxis or treatment of diabetes and the like.

This application is based on patent application Nos. 373776/2003, 30491/2004 and 165977/2004 filed in Japan, the contents of which are hereby incorporated by reference.

Claims

1. A compound represented by the formula



wherein

R^1 and R^2 are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted hydroxy group;

R^3 is an optionally substituted aromatic group;

R^4 is an optionally substituted amino group;

L is a divalent chain hydrocarbon group;

Q is a bond or a divalent chain hydrocarbon group; and

X is a hydrogen atom, a cyano group, a nitro group, an acyl group, a substituted hydroxy group, an optionally substituted thiol group, an optionally substituted amino group or an optionally substituted cyclic group;

provided that

when X is an ethoxycarbonyl group, then Q is a divalent chain hydrocarbon group, and that the compound is not 2,6-diisopropyl-3-methylaminomethyl-4-(4-fluorophenyl)-5-pentylpyridine;

2,6-diisopropyl-3-aminomethyl-4-(4-fluorophenyl)-5-pentylpyridine;

2,6-diisopropyl-3-(dimethylamino)methyl-4-(4-fluorophenyl)-5-pentylpyridine;

2,6-diisopropyl-3-(ethylamino)methyl-4-(4-fluorophenyl)-5-pentylpyridine; and

3-(tert-butyldimethylsilyloxymethyl)-2,6-diisopropyl-4-(4-fluorophenyl)-5-(indolyl-5-aminomethyl)pyridine,

or a salt thereof.

2. The compound of claim 1, wherein R^1 and R^2 are the same or different and each is an optionally substituted hydrocarbon group, and X is a cyano group, a nitro group, an acyl group, a substituted hydroxy group, an optionally substituted thiol group or an optionally substituted cyclic group.

3. The compound of claim 1, wherein the acyl group for X is a carboxyl group.

4. The compound of claim 1, wherein R^1 and R^2 are the same or different and each is a C_{1-10} alkyl group optionally substituted by 1 to 3 substituent(s) selected from a C_{3-10} cycloalkyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkoxy group.

5. The compound of claim 1, wherein R^3 is a C_{6-14} aryl group optionally substituted by 1 to 3 substituent(s) selected from a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atom(s) and a halogen atom.

6. The compound of claim 1, wherein R^4 is an amino group.

7. The compound of claim 1, wherein L is a C_{1-10} alkylene group.

8. The compound of claim 1, wherein Q is a bond.

9. The compound of claim 1, wherein X is an acyl group, a substituted hydroxy group, an optionally substituted thiol group or an optionally substituted amino group.

10. The compound of claim 1, wherein X is a carboxyl group.

11. The compound of claim 1, which is 5-(aminomethyl)-2-methyl-4-(4-methylphenyl)-6-neopentylnicotinic acid;
5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)nicotinic acid;
methyl 3-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy}-1-methyl-1H-pyrazole-4-carboxylate;
{[2-isobutyl-6-methyl-4-(4-methylphenyl)-5-(2-morpholin-4-yl-2-oxoethyl)pyridin-3-yl]methyl}amine;
methyl 3-({[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]acetyl}amino)benzoate;
N-[5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]isoxazole-4-carboxamide,
or a salt thereof.

12. A prodrug of a compound of claim 1 or a salt thereof.

13. A pharmaceutical agent comprising a compound of claim 1 or a salt thereof or a prodrug thereof.

14. The pharmaceutical agent of claim 13, which is an agent for the prophylaxis or treatment of diabetes, diabetic complications, impaired glucose tolerance or obesity.

15. A peptidase inhibitor comprising a compound of claim 1 or a salt thereof or a prodrug thereof.

16. The inhibitor of claim 15, wherein the peptidase is dipeptidyl dipeptidase-IV.

17. Use of a compound of claim 1 or a salt thereof or a prodrug thereof for the production of an agent for the prophylaxis or treatment of diabetes, diabetic complications, impaired glucose tolerance or obesity.

18. Use of a compound of claim 1 or a salt thereof or a prodrug thereof for the production of a peptidase inhibitor.

19. A method for the prophylaxis or treatment of diabetes, diabetic complications, impaired glucose tolerance or obesity in a mammal, which comprises administering a compound of claim 1 or a salt thereof or a prodrug thereof to the mammal.

20. A method of inhibiting peptidase in a mammal, which comprises administering a compound of claim 1 or a salt thereof or a prodrug thereof to the mammal.

21. A production method of a compound represented by the formula

(I-a)

wherein

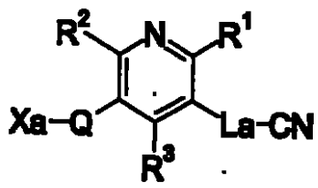
R^1, R^2, R^3 and Q

are as defined in claim 1;

La is a bond or a divalent chain hydrocarbon group; and

Xa is a hydrogen atom, a nitro group, an acyl group, a substituted hydroxy group, an optionally substituted thiol group, an optionally substituted amino group or an optionally substituted cyclic group;

or a salt thereof, which comprises subjecting a compound represented by the formula



(II)

wherein each symbol is as defined above, or a salt thereof to a reduction reaction.

COMPUESTOS DE PIRIDINA

Campo técnico

La presente invención se refiere a un compuesto de piridina que posee actividad inhibitoria de peptidasa, el cual es útil como agente para profilaxis o tratamiento de diabetes y lo similar.

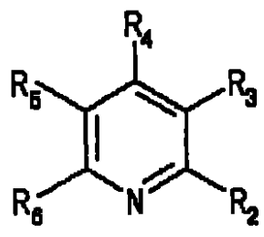
Técnica anterior

La peptidasa es conocida por que está relacionada con diversas enfermedades. La dipeptidil dipeptidasa-IV (más adelante en la presente a veces abreviado como DPP-IV), es un tipo de peptidasa, la cual es proteasa de serina que enlaza específicamente con un péptido que contiene prolina (o alanina) al segundo N-terminal y segmenta el lado C-terminal de la prolina (o alanina) para producir dipéptido. Se ilustra la DPP-IV por un molécula similar a CD26, y fue informado que también está involucrada en el sistema inmunológico. Mientras el papel de la DPP-IV en mamíferos no ha sido completamente esclarecido, se considera que juega un papel importante en el metabolismo de neuropéptidos, activación de células T, adherencia de células cancerosas a las células endoteliales, invasión del VIH en células y lo similar. Particularmente, desde el aspecto del glucometabolismo, la DPP-IV está involucrada en la inactivation de GLP-1 (péptido-1 similar a glucagón) y GIP (péptido inhibitorio gástrico/péptido insulinotrópico

dependiente de glucosa), las cuales son incretinas. Con respecto a GLP-1, además, se sabe que la actividad fisiológica de GLP-1 es disminuída notablemente porque posee una vida media de plasma breve de 1-2 minutos, y GLP-1(9-36)amida, que es un producto de degradación por DPP-IV, actúa en el receptor de GLP-1 como un antagonista, descomponiendo así GLP-1 por DPP-IV. También es conocido que la supresión de la degradación de GLP-1 por inhibición de la actividad de DPP-IV conduce a potenciación de la actividad fisiológica que presenta GLP-1, tal como efecto secretagogo de insulina dependiente de concentración de glucosa y lo similar. De estos hechos, se espera que un compuesto que posee una actividad inhibitoria de DPP-IV demuestre un efecto en tolerancia a glucosa disminuída, hiperglucosemia postprandial e hiperglucosemia de ayuno observada en la diabetes tipo I y tipo II y lo similar, obesidad o complicaciones del diabético asociadas con las mismas y lo similar.

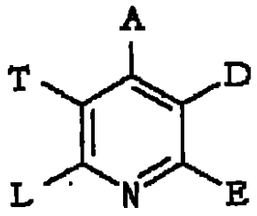
Como compuesto de piridina, se han informado los compuestos siguientes.

(1) un compuesto representado por la fórmula.



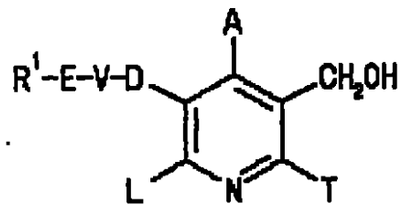
en donde R_2 y R_6 cada uno es independientemente hidrógeno, hidroxilo, alquilo y lo similar; R_3 es hidroxilo, amido y lo similar; R_4 es hidrógeno, hidroxilo, halógeno y lo similar; y R_5 es hidrógeno, hidroxilo, halógeno y lo similar que tiene una acción inhibitoria de proteína de transferencia colesterol • éster (más adelante en la presente abreviado como CETP) (ver WO99/41237).

(2) un compuesto representado por la fórmula.



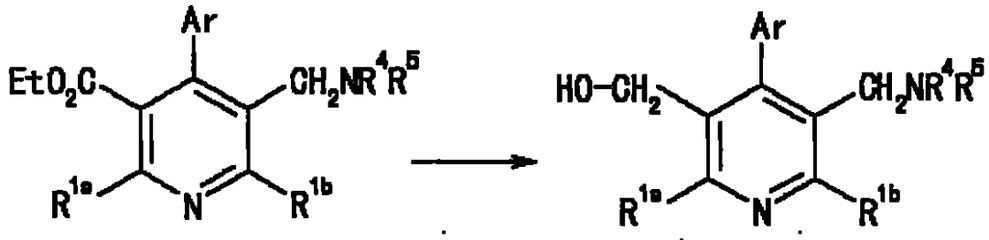
en donde A es arilo C_{6-10} opcionalmente sustituido por halógeno y lo similar; D es alquilo cadena lineal o ramificada que posee 8 o menos átomos de carbono opcionalmente sustituidos por hidroxilo; E y L son iguales o diferentes y cada uno es alquilo de cadena lineal o ramificada que tiene 8 o menos átomos de carbono opcionalmente sustituido por cicloalquilo C3-8, y lo similar; T es R^7-X- ó R^8-(R^9)(R^{10})C- (en donde R^7 y R^8 son iguales o diferentes y cada uno es cicloalquilo C_{3-8}, arilo C_{6-10} y lo similar; R^9 es hidrógeno y lo similar; R^{10} es hidrógeno, halógeno, azido y lo similar) que tiene una acción inhibitoria de CETP o una acción antagónica a glucagón;

un compuesto representado por la fórmula.



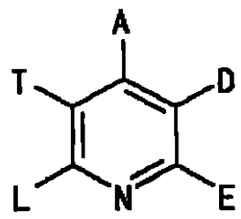
en donde A es arilo C_{6-10} opcionalmente sustituido por halógeno y lo similar; D y E son iguales o diferentes y cada uno es alquilo de cadena lineal o ramificada que posee 8 o menos átomos de carbono opcionalmente sustituidos por hidroxilo; V es O, S ó NR^5 (en donde R^5 es hidrógeno, alquilo de cadena lineal o ramificada que posee 6 ó menos átomos de carbono, o fenilo); R^1 es cicloalquilo C_{3-6}, arilo C_{6-10} y lo similar; L y T son iguales o diferentes y cada uno es trifluorometilo y lo similar; y

un compuesto representado por la fórmula.



en donde Ar es grupo aromático o heteroaromático opcionalmente sustituido; R^4 y R^5 son independientemente hidrógeno, alquilo C_{1-6} y lo similar; R^{1a} y R^{1b} son independientemente trifluorometilo, alquilo C_{1-6} y lo similar (ver WO98/04528, Patente Estadounidense No. 6218431).

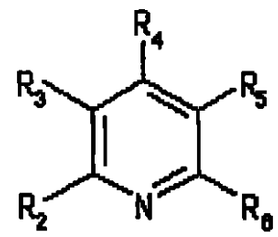
(3) Un compuesto representado por la fórmula



en donde A y E son iguales o diferentes y cada uno es opcionalmente arilo C_{6-10} sustituido por halógeno y lo similar; D es alquilo de cadena lineal o ramificada que posee 8 o menos átomos de carbono opcionalmente sustituidos por hidroxilo; L es cicloalquilo C_{3-8}, alquilo de cadena lineal o ramificada que posee 8 o menos átomos de carbono, y lo similar; T es R^3-X- ó R^4-(R^5)(R^6)C- (en donde R^3 y R^4 son iguales o diferentes y cada uno es cicloalquilo C_{3-8}, grupo arilo C_{6-10} y lo similar; R^5 es hidrógeno y lo similar; R^6 es hidrógeno, halógeno, azido y lo similar), o una sal del mismo, que posee una acción inhibitoria de CETP.

(ver patente Estadounidense No. 5925645).

(4) Un compuesto representado por la fórmula

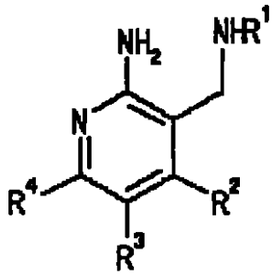


en donde R^2 y R^6 son independientemente bromoalquilo, cloroalquilo y lo similar; R^4 es alquilo, cicloalquilalquilo, alquiltioalquilo, cicloalquilo, alcoxialquilo o dialquilaminoalquilo; uno de R^3 y R^5 es CO-Y (en donde Y es

alquiltio, alcoxilo o grupo heterocíclico conteniendo N), el otro es -(-C(R^9)(R^{10})-)n-X (en donde n es un entero de valor 1-3; R^9 y R^{10} son independientemente hidrógeno, alquilo y lo similar; X es halógeno, OH y lo similar) y lo similar, o una sal del mismo que posee una acción herbicida

(ver WO92/20659).

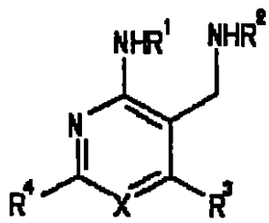
(5) Un compuesto representado por la fórmula.



en donde R^1 es hidrógeno o alquilo inferior; R^2 es grupo heterocíclico o arilo cada uno opcionalmente sustituido por alquilo inferior y lo similar; R^3 y R^4 pueden formar un anillo fenilo y lo similar cada uno opcionalmente sustituido por halógeno y lo similar, junto con los átomos de carbono unidos a los mismos, o una sal del mismo que posee una acción inhibitoria de DPP-IV

(ver WO03/068748).

(6) un compuesto representado por la fórmula



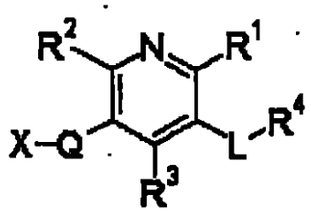
en donde X es N ó CR^5 (en donde R^5 es hidrógeno o alquilo inferior); R^1 y R^2 son independientemente hidrógeno o alquilo inferior; R^3 es grupo heterocíclico o arilo cada uno opcionalmente sustituido por alquilo inferior y lo similar; R^4 es alquilo inferior y lo similar, o una sal del mismo que posee una acción inhibitoria de DPP-IV (ver WO03/068757).

Sin embargo, no hay ningún informe sobre el compuesto de la presente invención.

Descripción de la invención

Se produjo la demanda del desarrollo de un compuesto que posea una acción inhibitoria de peptidasa que sea útil como agente para profilaxis o tratamiento de diabetes y lo similar y sea superior en eficacia, duración de acción, especificidad, toxicidad inferior y lo similar.

Los presentes inventores han encontrado primero que un compuesto representado por la fórmula



(I)

en donde

R^1 y R^2 son iguales o diferentes y cada uno es un grupo de hidrocarburo opcionalmente sustituido o un grupo hidroxilo

opcionalmente sustituido;

R^3 es un grupo aromático opcionalmente sustituido;

R^4 es un grupo amino opcionalmente sustituido;

L es un grupo de hidrocarburo de cadena bivalente;

Q es un enlace o un grupo hidrocarburo de cadena bivalente; y

X es un átomo de hidrógeno, un grupo ciano, un grupo nitro, un grupo acilo, un grupo hidroxilo sustituido, un grupo tiol opcionalmente sustituido, un grupo amino opcionalmente sustituido o un grupo cíclico opcionalmente sustituido;

con la condición que

cuando X es un grupo etoxicarbonilo, entonces Q es un grupo hidrocarburo de cadena bivalente, y el compuesto no es

2,6-diisopropil-3-metilaminometil-4-(4-fluorofenil)-5-pentilpiridina;

2,6-diisopropil-3-aminometil-4-(4-fluorofenil)-5-pentilpiridina;

2,6-diisopropil-3-(dimetilamino)metil-4-(4-fluorofenil)-5-pentilpiridina;

2,6-diisopropil-3-(etilamino)metil-4-(4-fluorofenil)-5-pentilpiridina; y

3-(terc-butildimetilsililoximetil)-2;6-diisopropil-4-(4-fluorofenil)-5-(indolil-5-aminometil)piridina;

o una sal del mismo.

[más adelante en la presente a veces aberviado como compuesto (I)] que se caracteriza por una estructura química en donde un grupo amino opcionalmente sustituido está enlazado en la posición 3 del anillo piridina mediante un grupo hidrocarburo de cadena bivalente y un grupo aromático opcionalmente sustituido se enlaza en la posición 4, posee una acción inhibitoria de peptidasa superior y es útil como agente para la profilaxis o tratamiento de diabetes y lo similar. Basados en este hallazgo, los presentes inventores han conducido estudios intensivos y han completado la presente invención.

Concordantemente, la presente invención se refiere a

1) compuesto (I);

2) compuesto (I), en donde R^1 y R^2 son iguales o diferentes y cada uno es un grupo hidrocarburo opcionalmente sustituido, y X es un grupo ciano, un grupo nitro, un grupo acilo, un grupo hidroxilo sustituido, un grupo tiol opcionalmente sustituido o un grupo cíclico opcionalmente sustituido;

3) compuesto (I), en donde el grupo acilo para X es un grupo carbonilo;

4) compuesto (I), en donde R^1 y R^2 son iguales o diferentes y cada uno es opcionalmente un grupo alquilo C1-10 sustituido por 1 a 3 sustituyente(s) seleccionado de un grupo cicloalquilo C_{3-10}, un grupo alcoxicarbonilo C_{1-6} y un grupo alcoxilo C_{1-6};

5) compuesto (I), en donde R^3 es un grupo arilo C_{6-14} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado de un grupo alquilo C1-6 opcionalmente sustituido por 1 a 3 átomo(s) halógenos y un átomo halógeno;

6) compuesto (I), en donde R^4 es un grupo amino;

7) compuesto (I), en donde L es un grupo alquileno C_{1-10};

8) compuesto (I), en donde Q es un enlace;

9) compuesto (I), en donde X es un grupo acilo, un es un grupo hidroxilo sustituido, un grupo tiol opcionalmente sustituido o un grupo amino opcionalmente sustituido;

10) compuesto (I), en donde X es un grupo carbonilo;

11) compuesto (I) es ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico;

ácido 5-(aminometil)-6-isobutílico-2-metil-4-(4-metilfenil)nicotínico;

metil 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxilato;

{[2-isobutil-6-metil-4-(4-metilfenil)-5-(2-morfolin-4-il-2-oxoetil)piridin-3-il]metil}amina;

metil 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoato;

N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]isoxazol-4-carboxamida,

o una sal del mismo;

12) una prodroga del compuesto (I);

13) un agente farmacéutico que comprende el compuesto (I) o una prodroga del mismo;

14) un agente farmacéutico del 13) precedentemente que es un agente para la profilaxis o tratamiento de diabetes, complicaciones diabéticas, tolerancia de glucosa disminuída u obesidad;

15) un inhibidor de peptidasa que comprende al compuesto (I) o una prodroga del mismo;

16) el inhibidor de 15) precedentemente, en donde la peptidasa es dipeptidil dipeptidasa-IV;

17) la utilización del compuesto (I) o una prodroga del mismo para la producción de un agente para profilaxis o tratamiento de diabetes, complicaciones diabéticas, tolerancia de glucosa disminuída u obesidad;

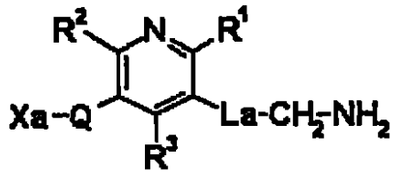
18) la utilización del compuesto (I) o una prodroga del mismo para la producción de un inhibidor de peptidasa;

19) un método para profilaxis o tratamiento de diabetes, complicaciones diabéticas, tolerancia de glucosa disminuída u obesidad en un mamífero que comprende administrar el compuesto (I) o una prodroga del mismo al mamífero;

20) un método para inhibir la peptidasa en un mamífero que comprende administrar el compuesto (I) o una prodroga del mismo al mamífero;

21) un método de producción de un compuesto representado por

la fórmula



(I-a)

en donde

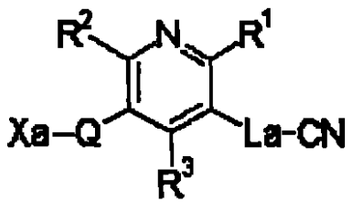
R^1, R^2, R^3 y Q

son iguales a los definidos en el compuesto (I);

La es un enlace o un grupo de hidrocarburo de cadena bivalente; y

Xa es un átomo de hidrógeno, un grupo nitro, un grupo acilo, un grupo hidroxilo sustituido, un grupo tiol opcionalmente sustituido, un grupo amino opcionalmente sustituido o un grupo cíclico opcionalmente sustituido;

o una sal del mismo que comprende someter un compuesto representado por la fórmula.



(II)

en donde cada simbolo es igual al definido anteriormente, o una sal del mismo a una reacción de reducción; y lo similar.

El compuesto de la presente invención posee una acción

inhibitoria de peptidasa superior y es útil como agente para profilaxis o tratamiento de diabetes y lo similar.

Mejor modalidad para la realización de la invención

Cada símbolo en la fórmula (I) se describe en detalle a continuación.

Como el "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para R^1 ó R^2, por ejemplo, puede mencionarse un grupo alquilo C_{1-10}, un grupo alquenilo C_{2-10}, un grupo alquinilo C_{2-10}, un grupo cicloalquilo C_{3-10}, un grupo cicloalquenilo C_{3-10}, un grupo cicloalcadienilo C_{4-10}, un grupo arilo C_{6-14}, un grupo aralquilo C_{7-13}, un grupo arilalquenilo C_{8-13}, un grupo cicloalquil C_{3-10}-alquilo C_{1-6} y lo similar.

Como el grupo alquilo C_{1-10} en la presente, por ejemplo, puede mencionarse metilo, etilo, propilo, isopropilo, butilo, isobutílico, sec-butilo, terc-butilo, pentilo, isopentilo, neopentilo, 1-etilpropilo, hexilo, isohexilo, 1,1-dimetilbutilo, 2,2-dimetilbutilo, 3,3-dimetilbutilo, 2-etilbutilo, heptilo, octilo, nonilo, decilo y lo similar.

Como grupo alquenilo C_{2-10}, por ejemplo, puede mencionarse 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 lo similar.

Como grupo alquinilo C_{2-10}, por ejemplo, puede mencionarse 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 lo similar.

Como grupo cicloalquilo C_{3-10}, por ejemplo, puede mencionarse cyclopropilo, 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 y lo similar.

Como grupo cicloalquenilo C_{3-10}, por ejemplo, puede mencionarse 2-ciclopenten-1-ilo, 3-ciclopenten-1-ilo, 2-ciclohexen-1-ilo, 3-ciclohexen-1-ilo y lo similar.

Como grupo cicloalcadienilo C_{4-10}, por ejemplo, puede mencionarse 2,4-ciclopentadien-1-ilo, 2,4-ciclohexadien-1-ilo, 2,5-ciclohexadien-1-ilo y lo similar.

Como grupo arilo C_{6-14}, por ejemplo, puede mencionarse fenilo, naftilo, antrilo, fenantirilo, acenaftilenilo, bifenililo y lo similar. De éstos, es preferible fenilo, 1-naftilo, 2-naftilo y lo similar.

Como grupo aralquilo C_{7-13}, por ejemplo, puede mencionarse bencilo, fenetilo, naftilmetilo, bifenililmetilo y lo similar.

Como grupo arilalquenilo C_{8-13}, por ejemplo, puede mencionarse estirilo y lo similar.

Como grupo cicloalquil C_{3-10}-alquilo C_{1-6}, por ejemplo, puede mençionarse ciclohexilmetilo y lo similar.

El grupo alquilo C_{1-10} mencionado, grupo alquenilo C_{2-10} y grupo alquinilo C_{2-10} opcionalmente posee 1 a 3 sustituyente(s) en posición(es) sustituible(s).

Como estos sustituyentes, por ejemplo.

(1) un grupo cicloalquilo C_{3-10} (por ejemplo, ciclopropilo, ciclohexilo);

(2) un grupo arilo C_{6-14} (por ejemplo, fenilo, naftilo);

(3) un grupo heterocíclico aromático (por ejemplo, tienilo, furilo, piridilo, oxazolilo, tiazolilo, tetrazolilo, oxadiazolilo, pirazinilo, quinolilo, indolilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionados de un grupo carbonilo, un grupo carbamoilo, un grupo tiocarbamoilo y un grupo alcoxicarbonilo C_{1-6} (por ejemplo, metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, terc-butoxicarbonilo);

(4) un grupo heterocíclico no aromático (por ejemplo, tetrahidrofurilo, morfolino, tiomorfolino, piperidino, pirrolidinilo, piperazinilo, oxodioxolilo, oxodioxolanilo, oxo-2-benzofuranilo, oxooxadiazolilo) opcionalmente sustituido por un grupo alquilo C_{1-6} (por ejemplo, metilo, etilo);

(5) un grupo amino opcionalmente mono- o di-sustituido por

sustituyente(s) seleccionados de un grupo alquilo C_{1-6} (por ejemplo, metilo, etilo), un grupo alquil C_{1-6}-carbonilo (por ejemplo, acetilo, isobutanoilo, isopentanoilo) y un grupo alcoxicarbonilo C_{1-6} (por ejemplo, metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, terc-butoxicarbonilo);

(6) un grupo alquilsulfonilamino C_{1-6} (por ejemplo, metilsulfonilamino);

(7) un grupo amidino;

(8) un grupo alquil C_{1-6}-carbonilo (por ejemplo, acetilo, isobutanoilo, isopentanoilo);

(9) un grupo alcoxicarbonilo C_{1-6} (por ejemplo, metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, terc-butoxicarbonilo);

(10) un grupo alquilsulfonilo C_{1-6} (por ejemplo, metilsulfonilo);

(11) un grupo carbamoilo opcionalmente mono- o di-sustituido por un grupo alquilo C_{1-6} (por ejemplo, metilo, etilo) opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo);

(12) un grupo tiocarbamoilo opcionalmente mono- o di-sustituido por un grupo alquilo C_{1-6} (por ejemplo, metilo, etilo) opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo);

(13) un grupo sulfamoilo opcionalmente mono- o di-sustituido por un grupo alquilo C_{1-6} (por ejemplo, metilo, etilo)

opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo);

(14) un grupo carbonilo;

(15) un grupo hidroxilo;

(16) un grupo alcoxilo C_{1-6} (por ejemplo, metoxilo, etoxilo) opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo);

(17) un grupo alqueniloxilo C2-6 (por ejemplo, eteniloxilo) opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo);

(18) un grupo cicloalquiloxilo C3-10 (por ejemplo, ciclohexiloxilo);

(19) un grupo aralquiloxilo C7-13 (por ejemplo, benciloiloy);

(20) un grupo ariloxilo C6-14 (por ejemplo, feniloxilo, naftiloxilo);

(21) un grupo alquil C1-6-carboniloxilo (por ejemplo, acetiloxilo, terc-butilcarboniloxilo);

(22) un grupo tiol;

(23) un grupo alquiltio C_{1-6} (por ejemplo, metiltio, etiltio) opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo);

(24) un grupo aralquiltio C_{7-13} (por ejemplo, benciltio);

(25) un grupo ariltio C_{6-14} (por ejemplo, feniltio, naftiltio);

(26) un grupo sulfo;

(27) un grupo ciano;

(28) un grupo azido;

(29) un grupo nitro;

(30) un grupo nitroso;

(31) un átomo halógeno (por ejemplo, flúor, cloro, bromo, iodo);

(32) un grupo alquilsulfinilo C_{1-6} (por ejemplo, metilsulfinilo);

y lo similar puede mencionarse.

El grupo cicloalquilo C_{3-10}, grupo cicloalquenilo C_{3-10}, grupo cicloalcadienilo C_{4-10}, grupo arilo C_{6-14}, grupo aralquilo C_{7-13}, grupo arilalquenilo C_{8-13} y grupo cicloalquil C_{3-10}-alquilo C_{1-6}, los cuales se indican de manera ejemplar como el "grupo hidrocarburo" mencionado opcionalmente poseen 1 a 3 sustituyente(s) en posición(es) sustituibles.

Como estos sustituyentes, por ejemplo,

los indicados de manera ejemplar para sustituyentes del grupo alquilo C_{1-10} indicado y lo similar;

un grupo alquilo C_{1-6} (por ejemplo, metilo, etilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionados de un átomo halógeno (por ejemplo, flúor, cloro, bromo, iodo), un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} (por ejemplo, metoxicarbonilo, etoxicarbonilo) y un grupo carbamoilo;

un grupo alquenilo C_{2-6} (por ejemplo, etenilo, 1-propenilo) opcionalmente sustituido por 1 a 3 sustituyente(s)

seleccionados de un átomo halógeno (por ejemplo, flúor, cloro, bromo, iodo), un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} (por ejemplo, metoxicarbonilo, etoxicarbonilo) y un grupo carbamoilo;

un grupo aralquilo C_{7-13} (por ejemplo, bencilo); y lo similar puede mencionarse.

El "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para R^1 o R^2 es preferentemente un grupo alquilo C_{1-10}, un grupo arilo C_{6-14} o un grupo aralquilo C_{7-13}, más preferentemente un grupo alquilo C_{1-10}.

El "grupo hidrocarburo opcionalmente sustituido" para R^1 ó R^2 es preferentemente

(1) un grupo alquilo C_{1-10} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado de un grupo cicloalquilo C_{3-10}, un grupo alcoxicarbonilo C_{1-6}, un grupo alcoxilo C_{1-6} y lo similar;

(2) un grupo arilo C_{6-14} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado de un átomo halógeno, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6}, un grupo carbamoilo y lo similar; o

(3) un grupo aralquilo C_{7-13}.

De éstos, es preferible un grupo alquilo C_{1-10} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionados de un grupo cicloalquilo C_{3-10}, un grupo alcoxicarbonilo C_{1-6}, un grupo alcoxilo C_{1-6} y lo similar.

Como el "grupo hidroxilo sustituido" del "gruupo hidroxilo opcionalmente sustituido" para R^1 ó R^2, pueden usarse aquéllos ejemplarmente indicados para X más adelante.

R^1 y R^2 son preferentemente cada uno un "grupo hidrocarburo opcionalmente sustituido", más preferentemente un grupo alquilo C_{1-10} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado de un grupo cicloalquilo C_{3-10}, un grupo alcoxicarbonilo C_{1-6}, un grupo alcoxilo C_{1-6} y lo similar.

Como el "grupo aromático" del "grupo aromático opcionalmente sustituido" para R^3, por ejemplo, puede mencionarse un grupo hidrocarburo aromático, un grupo heterocíclico aromático y lo similar.

Como grupo hidrocarburo aromático, por ejemplo, puede mencionarse un grupo arilo C_{6-14} que se indica de manera ejemplar para el "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para R^1 o R^2 mencionado, y lo similar.

Como el grupo heterocíclico aromático, por ejemplo, puede mencionarse un grupo heterocíclico aromático monocíclico de 5- a 7- miembros conteniendo 1 a 4 heteroátomo(s) seleccionado del átomo de oxigeno, átomo de azufre y átomo de nitrógeno como átomo constituyente de anillo, además de los átomos de carbono, y grupo heterocíclico aromático fusionado. Como el grupo

heterocíclico aromático fusionado, por ejemplo, puede mencionarse un grupo en donde estos grupos heterocíclicos aromáticos monocíclicos de 5- a 7- miembros y un anillo de 6- miembros que contiene 1 o 2 átom(s) de nitrógeno, un anillo de benceno o un anillo de 5- miembros que contienen un átomo de azufre son fusionados, y lo similar.

Como los ejemplos preferibles del grupo heterocíclico aromático,

los 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, 6-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, oxazolilo (por ejemplo, 2-oxazolilo, 4-oxazolilo, 5-oxazolilo), 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) y lo similar;

grupos heterocíclicos aromáticos fusionados tales como quinolilo (por ejemplo, 2-quinolilo, 3-quinolilo, 4-quinolilo), quinazolilo (por ejemplo, 2-quinazolilo, 4-quinazolilo), quinoxalilo (por ejemplo, 2-quinoxalilo), benzofurilo (por ejemplo, 2-benzofurilo, 3-benzofurilo), benzotienilo (por ejemplo, 2-benzotienilo, 3-benzotienilo), benzoxazolilo (por ejemplo, 2-benzoxazolilo), benzotiazolilo (por ejemplo, 2-benzotiazolilo), benzimidazolilo (por ejemplo, benzimidazol-1-ilo, benzimidazol-2-ilo), indolilo (por ejemplo, indol-1-ilo, indol-3-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), imidazopirazinilo (por ejemplo, 1H-imidazo[4,5-b]pirazin-2-ilo) y lo similar,

y lo similar puede mencionarse.

El "grupo aromático" del "grupo aromático opcionalmente sustituido" para R^3 es preferentemente un grupo hidrocarburo aromático, más preferentemente un grupo arilo C_{6-14}, aún más preferentemente fenilo.

El "grupo aromático" del "grupo aromático opcionalmente

sustituido" para R^3 posee opcionalmente 1 a 3 sustituyente(s) en posición(es) sustituible(s).

Como estos sustituyentes, por ejemplo, pueden mencionarse aquéllos indicados a manera de ejemplo para sustituyentes de grupo cicloalquilo C_{3-10} indicado para el "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para R^1 ó R^2 indicado a manera de ejemplo.

Los sustituyentes son preferentemente

un grupo alquilo C_{1-6} opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo);

un átomo halógeno (por ejemplo, flúor, cloro, bromo, iodo);

un grupo alcoxicarbonilo C_{1-6};

un grupo carboxilo;

un grupo hidroxilo;

un grupo alcoxilo C_{1-6} opcionalmente sustituido por 1 a 3 átomo(s) halógenos;

y lo similar, más preferentemente

un grupo alquilo C_{1-6} (por ejemplo, metilo, etilo) opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo);

un átomo halógeno (por ejemplo, flúor, cloro, bromo, iodo);

y lo similar.

El "grupo aromático opcionalmente sustituido" para R^3 es

preferentemente un grupo arilo C_{6-14} (en donde el grupo arilo C_{6-14} es preferentemente un fenilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionados de un grupo alquilo C_{1-6} (por ejemplo, metilo, etilo) opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo), un átomo halógeno (por ejemplo, flúor, cloro, bromo, iodo), y lo similar.

Como el "grupo amino opcionalmente sustituido" por R^4, por ejemplo, puede mencionarse un grupo amino opcionalmente sustituido por 1 o 2 sustituyente(s) seleccionados de un grupo alquilo C_{1-10}, un grupo alquenilo C_{2-10}, un grupo cicloalquilo C_{3-10}, un grupo cicloalquenilo C_{3-10}, un grupo arilo C_{6-14}, un grupo aralquilo C_{7-13} y un grupo arilalquenilo C_{8-13} cada uno de los cuales es opcionalmente sustituido; un grupo acilo y lo similar.

Como el grupo alquilo C_{1-10}, pueden usarse grupo alquenilo C_{2-10}, grupo cicloalquilo C_{3-10}, grupo cicloalquenilo C_{3-10}, grupo arilo C_{6-14}, grupo aralquilo C_{7-13} y grupo arilalquenilo C_{8-13} en la presente, aquéllos indicados a manera de ejemplo para el "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para los mencionados precedentemente R^1 ó R^2.

Estos grupos alquilo C_{1-10}, grupo alquenilo C_{2-10}, grupo cicloalquilo C_{3-10}, grupo cicloalquenilo C_{3-10}, grupo arilo C_{6-14}, grupo aralquilo C_{7-13} y grupo arilalquenilo C_{8-13} cada uno

opcionalmente tiene 1 a 3 sustituyente(s) en posición(es) sustituible(s). Como estos sustituyentes, por ejemplo, puede mencionarse

un átomo halógeno (por ejemplo, flúor, cloro, bromo, iodo);

un grupo alcoxicarbonilo C_{1-6} (por ejemplo, metoxicarbonilo, etoxicarbonilo, terc-butoxicarbonilo);

un grupo alquil C_{1-6}-carbonilo;

un grupo ciano;

un grupo carbamoilo opcionalmente mono- o di-sustituido por un grupo alquilo C_{1-10} (por ejemplo, metilo, etilo, propilo, isopropilo, neopentilo);

un grupo hidroxilo;

un grupo carboxilo;

y lo similar.

Como los grupos acilo indicados para sustituyentes del "grupo amino opcionalmente sustituido", pueden usarse aquéllos indicados a manera de ejemplo para X más adelante. De éstos,

(1) un grupo alquil C_{1-6}-carbonilo (por ejemplo, acetilo, isobutanoilo, isopentanoilo);

(2) un grupo alcoxicarbonilo C_{1-6} (por ejemplo, metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, terc-butoxicarbonilo) opcionalmente sustituido por un grupo alcoxicarbonilo C_{1-6};

(3) un grupo cicloalquil C_{3-10}-carbonilo (por ejemplo, ciclopentilcarbonilo, ciclohexilcarbonilo);

(4) un grupo aril C_{6-14}-carbonilo (por ejemplo, benzoilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un átomo halógeno, un grupo ciano, un opcionalmente grupo alquilo C_{1-6} halogenado, un grupo alcoxilo C_{1-6}, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6}, un grupo heterocíclico aromático (por ejemplo, tetrazolilo, oxadiazolilo), un grupo heterocíclico no aromático (por ejemplo, oxooxadiazolilo) y un grupo carbamoilo;

(5) un grupo aralquiloxi C_{7-13}-carbonilo (por ejemplo, benciloxicarbonilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(6) un grupo carbamoilo;

(7) un grupo mono- o di-alquil C_{1-6}-carbamoilo (por ejemplo, dimetilcarbamoilo);

(8) un grupo alquilsulfonilo C_{1-6} (por ejemplo, metilsulfonilo);

(9) un grupo arilsulfonilo C_{6-14} opcionalmente sustituido por un grupo alquilsulfonilo C_{1-6} (por ejemplo, fenilsulfonilo, metilsulfonilfenilsulfonilo);

(10) un grupo heterocíclico aromático (por ejemplo, piridilo, tiazolilo, oxazolilo, indolil) - sulfonilo opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un

grupo alquilo C_{1-6} y un grupo mono- o dialquil C_{1-6}-carbonil)-amino (por ejemplo, 2-acetilamino-4-metil-5-tiazolilsulfonilo);

(11) un grupo aralquil C_{7-13}-carbonilo (por ejemplo, bencilcarbonilo, fenetilcarbonilo);

(12) un grupo arilalquenil C_{8-13}-carbonilo (por ejemplo, estirilcarbonilo);

(13) un grupo heterociclico aromático (por ejemplo, furil, tienil, oxazolil, tiazolil, isoxazolil, isotiazolil, pirazolil, piridil, pirazinil, benzofuril, benzotienil, quinoxalinil)-carbonilo (por ejemplo, furilcarbonilo, tienilcarbonilo, tiazolilcarbonilo, pirazolilcarbonilo, piridilcarbonilo, pirazinilcarbonilo, benzofurilcarbonilo, benzotienilcarbonilo, quinoxalinilcarbonilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6}, un grupo arilo C_{6-14}, un grupo aralquilo C_{7-13}, un grupo alcoxilo C_{1-6}, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(14) un grupo heterociclico (por ejemplo, pirrolidinil, piperidinil, piperazinil, morfolin, oxopiperazinil)-carbonilo conteniendo nitrógeno opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6} (el grupo alquilo C1-6 es opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionados de grupo carbonilo, grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo), un grupo

carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(15) un grupo aril C_{6-14}-heterociclico conteniendo nitrógeno (por ejemplo, pirrolidinil, piperidinil, piperazinil, morfolin)-carbonilo;

(16) un grupo 4-oxo-4,5,6,7-tetrahidro-1-benzofuranil-carbonilo;

(17) un grupo tetrahidropiranilcarbonilo;

(18) un grupo ariloxi C_{6-14}-carbonilo opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(19) un grupo aralquil-carbamoilo C_{7-13} (por ejemplo, bencilcarbamoilo);

(20) un grupo heterociclico aromático (por ejemplo, piridilo, tiazolil, oxazolilo, indolil)-carbamoilo (por ejemplo, tiazolilcarbamoilo, oxazolilcarbamoilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionados de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

y lo similar, es preferible.

Como los ejemplos preferibles del grupo amino sustituido,

(1) un grupo mono- o dialquilamino C_{1-10} (por ejemplo, metilamino, dimetilamino, etilamino, dietilamino,

propilamino, dibutilamino);

(2) un grupo mono- o dialquenilamino C_{2-10} (por ejemplo, dialilamino);

(3) un grupo mono- o di-cicloalquilamino C_{3-10} (por ejemplo, ciclohexilamino);

(4) un grupo arilamino C_{6-14} (por ejemplo, fenilamino);

(5) un grupo mono- o di-(alquil C_{1-6}-carbonil)-amino (por ejemplo, acetilamino, propionilamino, butanoilamino, isobutanoilamino, isopentanoilamino);

(6) un grupo alcoxi C_{1-6}-carbonilamino (por ejemplo, metoxicarbonilamino) opcionalmente sustituido por grupo alcoxicarbonilo C_{1-6};

(7) un grupo carbamoil-alquilamino C_{1-10} (por ejemplo, carbamoilmetilamino);

(8) un grupo alcoxi C_{1-6}-carbonil-alquilamino C_{1-10} (por ejemplo, metoxicarbonilmetilamino, etoxicarbonilmetilamino, terc-butoxicarbonilmetilamino);

(9) un grupo carboxi-alquilamino C_{1-10} (por ejemplo, carboximetilamino);

(10) un grupo cicloalquil C_{3-10}-carbonilamino (por ejemplo, ciclopentilcarbonilamino, ciclohexilcarbonilamino);

(11) un grupo aril C_{6-14}-carbonilamino (por ejemplo, benzoilamino) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un átomo halógeno, un grupo ciano, un grupo alquilo C_{1-6} opcionalmente halogenado,

un grupo alcoxilo C_{1-6}, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6}, un grupo heterocíclico aromático (por ejemplo, tetrazolilo, oxadiazolilo), un grupo heterocíclico no aromático (por ejemplo, oxooxadiazolilo) y un grupo carbamoilo;

(12) un grupo aralquiloxi C_{7-13}-carbonilamino (por ejemplo, benciloxicarboniloamino) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(13) un grupo carbamoiloamino;

(14) un grupo mono- o dialquil C_{1-6}-carbamoiloamino (por ejemplo, dimetilcarbamoilamino);

(15) un grupo alquilsulfonilamino C_{1-6} (por ejemplo, metilsulfonilamino);

(16) un grupo arilsulfonilamino C_{6-14} opcionalmente sustituido por un grupo alquilsulfonilo C_{1-6} (por ejemplo, fenilsulfonilamino, metilsulfonilfenilsulfonilamino);

(17) un grupo heterocíclico aromático (por ejemplo, piridil, tiazolil, oxazolil, indolil)-sulfonilamino opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6} y un grupo mono- o dialquil C_{1-6}-carbonil)-amino (por ejemplo, 2-acetilamino-4-metil-5-tiazolilsulfonilamino);

(18) un grupo aralquil C_{7-13}-carbonilamino (por ejemplo, bencilcarbonilamino, fenetilcarbonilamino);

(19) un grupo arilalquenil C_{8-13}-carbonilamino (por ejemplo, estirilcarbonilamino);

(20) un grupo heterocíclico aromático (por ejemplo, furil, tienil, oxazolil, tiazolil, isoxazolil, isotiazolil, pirazolil, piridil, pirazinil, benzofuril, benzotienil, quinoxalinil)-carbonilamino opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6}, un grupo arilo C_{6-14}, un grupo aralquilo C_{7-13}, un grupo alcoxilo C_{1-6}, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(21) un grupo heterocíclico conteniendo nitrógeno (por ejemplo, pirrolidinil, piperidinil, piperazinil, morfolin, oxopiperazinil)-carbonilamino opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6} (el grupo alquilo C_{1-6} es opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo), un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(22) un grupo aril C_{6-14}-heterocíclico conteniendo nitrógeno (por ejemplo, pirrolidinil, piperidinil, piperazinil, morfolin)-carbonilamino;

(23) un grupo tetrahidropiranilcarbonilamino;

(24) un grupo 4-oxo-4,5,6,7-tetrahidro-1-benzofuranil-carbonilamino;

(25) un grupo ariloxi C_{6-14}-carbonilamino opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(26) un grupo aralquil C_{7-13}-carbamoiloamino (por ejemplo, bencilcarbamoiloamino);

(27) un grupo heterocíclico aromático (por ejemplo, piridil, tiazolil, oxazolil, indolil)-carbamoilamino opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

y lo similar puede mencionarse.

El "grupo amino opcionalmente sustituido" para R^4 es preferentemente un grupo amino opcionalmente mono- o di-sustituido por un grupo alquilo C_{1-6} (por ejemplo, metilo, etilo, propilo, isopropilo). El R^4 es particularmente preferentemente un grupo amino.

Como el "grupo hidrocarburo de cadena bivalente" para L ó Q, por ejemplo, puede mencionarse un grupo hidrocarburo de cadena bivalente que posee 1 a 10 átomos de carbono. Los ejemplos específicos incluyen

(1) un grupo alquileno C_{1-10} (por ejemplo, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CHCH_3-$, $-C(CH_3)_2-$, $-(CH(CH_3))_2-$, $-(CH_2)_2C(CH_3)_2-$, $-(CH_2)_3C(CH_3)_2-$);

(2) un grupo alquenileno C_{2-10} (por ejemplo, $-CH=CH-$, $-CH_2-$

$CH=CH-$, $-CH=CH-CH_2-$, $-CH=CH-CH_2-CH_2-$, $-C(CH_3)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-CH=CH-CH=CH-$, $-CH=CH-CH_2-CH_2-CH_2-$);

(3) un grupo alquinileno C_{2-10} (por ejemplo, $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH_2-C\equiv C-CH_2-CH_2-$)

y lo similar.

El "grupo hidrocarburo de cadena bivalente" es preferentemente un grupo alquileno C_{1-10} o un grupo alquenileno C_{2-10}, más preferentemente $-CH_2-$, $-(CH_2)_2-$, $-CH=CH-$ y lo similar.

L es preferentemente un grupo alquileno C_{1-10}, más preferentemente $-CH_2-$ y lo similar.

Q es preferentemente un enlace, un grupo alquileno C_{1-10} o un grupo alquenileno C_{2-10}, más preferentemente un enlace, $-CH_2-$, $-(CH_2)_2-$, $-CH=CH-$ y lo similar. Q es preferentemente en particular un enlace.

Como "grupo acilo" para X, por ejemplo, un grupo representado por la fórmula: $-COR^5$, $-CO-OR^5$, $-SO_2R^5$, $-SOR^5$, $-PO_3R^5R^6$, $-CO-NR^{5a}R^{6a}$, $-C-NR^{5a}R^{6a}$ [en donde R^5 y R^6 son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo heterocíclico opcionalmente sustituido; R^{5a} y R^{6a} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo heterocíclico opcionalmente sustituido, o R^{5a} y R^{6a} pueden

formar un grupo heterocíclico opcionalmente sustituido conteniendo nitrógeno junto con átomo de nitrógeno adyacente], y lo similar puede mencionarse.

Como el "grupo hidrocarburo opcionalmente sustituido" para R^5, R^6, R^{5a} o R^{6a}, aquéllos indicados a manera de ejemplo para mencionados R^1 ó R2 pueden usarse.

Como el "grupo heterocíclico" del "grupo heterociclico opcionalmente sustituido" para R^5, R^6, R^{5a} ó R^{6a}, puede mencionarse un grupo heterocíclico aromático y un grupo heterociclico no aromático.

Como grupo heterocíclico aromático, pueden mencionarse aquéllos indicados a manera de ejemplo para "grupo aromático" del "grupo aromático opcionalmente sustituido" mencionado para R^3.

Como el grupo heterociclico no aromático, por ejemplo, puede mencionarse un grupo heterocíclico no aromático monocíclico de 5- a 7- miembros conteniendo 1 a 4 heteroátomo(s) seleccionado(s) del átomo de oxígeno, átomo de azufre y átomo de nitrógeno como átomo constituyente del anillo, además de los átomos de carbono, y un grupo heterocíclico no aromático fusionado. Como el grupo heterocíclico no aromático fusionado, por ejemplo, puede mencionarse un grupo en donde estos grupos heterocíclicos monocíclicos no aromáticos de 5- a 7- miembros y un anillo de 6 miembros que contiene 1 ó 2 átomo(s) de nitrógeno, un

anillo de benceno o un anillo de 5 miembros que contienen un átomo de azufre son fusionados, y lo similar.

Como los ejemplos preferibles del grupo heterocíclico no aromático, pyrrolidinilo (por ejemplo, 1-pirrolidinilo), piperidinilo (por ejemplo, piperidino), morfolinilo (por ejemplo, morfolino), tiomorfolinilo (por ejemplo, tiomorfolino), piperazinilo (por ejemplo, 1-piperazinilo), hexametileniminilo (por ejemplo, hexametilenimin-1-ilo), oxazolidinilo (por ejemplo, oxazolidin-3-ilo), tiazolidinilo (por ejemplo, tiazolidin-3-ilo), imidazolidinilo (por ejemplo, imidazolidin-3-ilo), oxoimidazolidinilo (por ejemplo, 2-oxoimidazolidin-1-ilo), dioxoimidazolidinilo (por ejemplo, 2,4-dioxoimidazolidin-3-ilo), dioxooxazolidinilo (por ejemplo, 2,4-dioxooxazolidin-3-ilo, 2,4-dioxooxazolidin-5-ilo, 2,4-dioxooxazolidin-1-ilo), dioxotiazolidinilo (por ejemplo, 2,4-dioxotiazolidin-3-ilo, 2,4-dioxotiazolidin-5-ilo), dioxoisoindolilo (por ejemplo, 1,3-dioxoisoindol-2-ilo), oxooxadiazolilo (por ejemplo, 5-oxooxadiazol-3-ilo), oxotiadiazolilo (por ejemplo 5-oxotiadiazol-3-ilo), oxopiperazinilo (por ejemplo, 3-oxopiperazin-1-ilo), dioxopiperazinilo (por ejemplo, 2,3-dioxopiperazin-1-ilo, 2,5-dioxopiperazin-1-ilo), oxodioxolilo (por ejemplo, 2-oxo-1,3-dioxol-4-ilo), oxodioxolanilo (por ejemplo, 2-oxo-1,3-dioxolan-4-ilo), oxo-2-benzofuranilo (por ejemplo, 3-oxo-2-benzofuran-1-ilo), oxodihidrooxadiazolilo (por ejemplo, 5-

oxo-4,5-dihidro-1,2,4-oxadiazol-3-ilo), 4-oxo-2-tioxo-1,3-tiazolidin-5-ilo, 4-oxo-2-tioxo-1,3-oxazolidin-5-ilo, tetrahidropiranilo (por ejemplo, 4-tetrahidropiranilo), 4-oxo-4,5,6,7-tetrahidro-1-benzofuranilo (por ejemplo, 4-oxo-4,5,6,7-tetrahidro-1-benzofuran-3-ilo), 1,3(2H,5H)-dioxo-tetrahidroimidazo[1,5-a]piridinilo, 1,3(2H,5H)-dioxo-10,10a-dihidroimidazo[1,5-b]isoquinolinilo y lo similar puede mencionarse

El "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para R^5, R^6, R^{5a} ó R^{6a} opcionalmente posee 1 a 3 sustituyente(s) en posición(es) sustituible(s)

Como estos sustituyentes, por ejemplo, pueden mencionarse aquéllos indicados a manera de ejemplo para sustituyentes de grupo cicloalquilo C_{3-10} indicados para el "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para R^1 o R2 mencionado a manera de ejemplo

Los sustituyentes son preferentemente

un grupo alquilo C_{1-6} (por ejemplo, metilo, etilo) opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, fluor, cloro, bromo, iodo),

un átomo halógeno (por ejemplo, flúor, cloro, bromo, iodo),

un grupo arilo C_{6-14},

un grupo aralquilo C_{7-13},

un grupo hidroxilo,

un grupo alcoxilo C1-6,

un grupo carboxilo,

un grupo alcoxicarbonilo C_{1-6},

un grupo carbamoilo,

un grupo alquilo C_{1-6} sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo,

un grupo mono- o dialquil C_{1-6}-carbonil)-amino,

y lo similar

Como el "heterociclo conteniendo nitrógeno del "heterocyclo conteniendo nitrógeno opcionalmente sustituido" formado por R^{5a} y R^{6a} junto con el átomo de nitrógeno adyacente, por ejemplo, un heterociclo conteniendo nitrógeno de 5- a 7- miembros conteniendo por lo menos un átomo de nitrógeno y conteniendo opcionalmente además 1 a 2 heteroátomo(s) seleccionado(s) del átomo de oxígeno, átomo de azufre y átomo de nitrógeno como un átomo constituyente del anillo, además de los átomos de carbono puede mencionarse Como los ejemplos preferibles del "heterociclo conteniendo nitrógeno", puede mencionarse tetrahidropirol, imidazolidina, pirazolidina, piperidina, piperazina, tetrahidrooxazina, tiomorfolina, oxopiperazina y lo similar

El heterociclo conteniendo nitrógeno opcionalmente posee 1 a 3 (preferentemente 1 ó 2) sustituyente(s) en posición(es) sustituible(s) Como estos sustituyentes, pueden mencionarse

un grupo hidroxilo,

un grupo alquilo C_{1-6} opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, fluor, cloro, bromo, iodo),

un grupo aralquilo C_{7-13} (por ejemplo, bencilo, difenilmetilo) opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, fluor, cloro, bromo, iodo),

un grupo arilo C_{6-14} (por ejemplo, fenilo) opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, fluor, cloro, bromo, iodo),

un grupo alcoxicarbonilo C_{1-6} (por ejemplo, metoxicarbonilo, etoxicarbonilo),

un grupo alquilo C_{1-6} sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo,

un grupo carboxilo,

un grupo carbamoilo,

y lo similar

Como los ejemplos preferibles del "grupo acilo", pueden mencionarse

(1) un grupo formilo,

(2) un grupo carbonilo,

(3) un grupo carbamoilo,

(4) un grupo alquil C_{1-6}-carbonilo (por ejemplo, acetilo, isobutanoilo, isopentanoilo),

(5) un grupo alcoxicarbonilo C_{1-6} opcionalmente sustituido por

1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo carbamoilo, un grupo tiocarbamoilo, un grupo alcoxicarbonilo C_{1-6} y un grupo alquil C_{1-6}-carboniloxilo (por ejemplo, metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, terc-butoxicarbonilo, carboximetoxicarbonilo, carboxietoxicarbonilo, carboxibutoxicarbonilo, carbamoilmetoxicarbonilo, tiocarbamoilmetoxicarbonilo, etoxicarbonilmetoxicarbonilo, etoxicarboniletoxicarbonilo, metoxicarbonilbutoxicarbonil, etoxicarbonilbutoxicarbonilo, terc-butilcarboniloximetoxicarbonilo),

(6) un grupo heterocíclico aromático (por ejemplo, furil, tienil, piridil, tiazolil, oxazolil, pirazinil, indolil)-alcoxi C_{1-6}-carbonilo opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de grupo carbonilo, grupo carbamoilo, grupo tiocarbamoilo y grupo alcoxi C_{1-6}-carbonilo (por ejemplo, piridilmetoxicarbonilo, carboxitiazolilmetoxicarbonilo, carbamoiltiazolilmetoxicarbonilo, etoxicarbonyltiazolilmetoxicarbonilo),

(7) un grupo heterocíclico no aromático (por ejemplo, oxodioxolil, oxodioxolanil, oxo-2-benzofuranil)-alcoxi C_{1-6}-carbonilo opcionalmente sustituido por un grupo alquilo C_{1-6} (por ejemplo, metiloxodioxolilmetoxicarbonilo, oxo-2-benzofuraniletoxicarbonilo),

(8) un grupo cicloalquil C_{3-10}-carbonilo (por ejemplo,

ciclopentilcarbonilo, ciclohexilcarbonilo),

(9) un grupo arıl C_{6-14}-carbonılo (por ejemplo, benzoılo, 1-naftoılo, 2-naftoılo) opcionalmente sustituıdo por 1 a 3 sustituyente(s) seleccıonado(s) de un átomo halógeno, un grupo cıano, un grupo alquılo C_{1-6} opcıonalmente halogenado (es decır, grupo alquılo C_{1-6} opcıonalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, fluor, cloro, bromo, ıodo)), un grupo alcoxılo C_{1-6}, un grupo carbonilo, un grupo alcoxıcarbonilo C_{1-6}, un grupo heterocíclico aromático (por ejemplo, tetrazolilo, oxadıazolılo), un grupo heterocíclico no aromático (por ejemplo, oxooxadiazolılo) y un grupo carbamoilo,

(10) un grupo arıloxı C_{6-14}-carbonılo (por ejemplo, fenıloxıcarbonılo, naftiloxıcarbonilo) opcıonalmente sustıtuıdo por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonılo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoılo,

(11) un grupo aralquıloxı C_{7-13}-carbonilo opcıonalmente sustituido por 1 a 3 sustituyente(s) seleccıonado(s) de un grupo carbonilo, un grupo carbamoilo, un grupo tıocarbamoilo, un grupo alcoxıcarbonılo C_{1-6}, un átomo halógeno, un grupo ciano, un grupo nıtro, un grupo alcoxilo C_{1-6}, un grupo alquılsulfonılo C_{1-6} y un grupo alquılo C_{1-6} (el grupo alquilo C_{1-6} es opcionalmente sustituido por 1 a 3 sustituyente(s) seleccıonado(s) de un átomo halógeno, un grupo carbonılo, un

grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo) (por ejemplo, benciloxicarbonilo, fenetiloxicarbonilo, carboxibenciloxicarbonilo, metoxicarbonilbenciloxicarbonilo, bifenililmetoxicarbonilo),

(12) un grupo carbamoilo mono- o disustituido por un grupo alquilo C1-6 opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de átomos halógenos (por ejemplo, fluor, cloro, bromo, iodo) y un grupo alcoxilo C_{1-6} (por ejemplo, metilcarbamoilo, etilcarbamoilo, dimetilcarbamoilo, dietilcarbamoilo, etilmetilcarbamoilo, propilcarbamoilo, isopropilcarbamoilo, butilcarbamoilo, isobutilcarbamoilo, trifluoroetilcarbamoilo, N-metoxietil-N-metilcarbamoilo),

(13) un grupo carbamoil-alquil C_{1-6}-carbamoilo opcionalmente mono- o disustituido por un grupo alquilo C_{1-6} opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo) (por ejemplo, carbamoilmetilcarbamoilo, carbamoiletilcarbamoilo, dimetilcarbamoilmetilcarbamoilo, dimetilcarbamoiletilcarbamoilo),

(14) un gruupo alcoxi C_{1-6}-carbonil-alquil C_{1-6}-carbamoilo opcionalmente sustituido por un grupo alquilo C1-6 (por ejemplo, metoxicarbonilmetilcarbamoilo, etoxicarboniletilcarbamoilo, N-etoxicarbonilmetil-N-metilcarbamoilo),

(15) un grupo aril C_{6-14}-carbamoilo (por ejemplo,

fenilcarbamoilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionados de un grupo amino opcionalmente mono- o disustituido por un grupo alquilo C_{1-6}, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6}, un grupo heterocíclico aromático (por ejemplo, tetrazolilo, oxadiazolilo), un grupo heterocíclico no aromático (por ejemplo, oxooxadiazolilo) y un grupo carbamoilo,

(16) un grupo mono- o dicicloalquil C_{3-10}-carbamoilo opcionalmente sustituido por un grupo alquilo C_{1-6} (por ejemplo, ciclopropilcarbamoilo, ciclopentilcarbamoilo, diciclohexilcarbamoilo, N-ciclohexil-N-metilcarbamoilo),

(17) un grupo aralquil C_{7-13}-carbamoilo opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un átomo halógeno (por ejemplo, fluor, cloro, bromo, iodo), un grupo hidroxilo, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo alquilo C_{1-6} (por ejemplo, bencilcarbamoilo, fenetilcarbamoilo, fenilpropilcarbamoilo, hidroxifenetilcarbamoilo, clorobencilcarbamoilo, metoxicarbonilbencilcarbamoilo, N-bencil-N-metilcarbamoilo),

(18) un grupo heterocíclico aromático (por ejemplo, piridil, tienil, furil, tiazolil, oxazolil, indolil)-alquil C_{1-6}-carbamoilo (por ejemplo, indoliletilcarbamoilo, piridilmetilcarbamoilo, tienilmetilcarbamoilo, tiazolilmetilcarbamoilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un

grupo carbamoilo y un grupo alcoxicarbonilo C_{1-6};

(19) un grupo alquilsulfonilo C_{1-6} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo carbamoilo y un grupo alcoxicarbonilo C_{1-6} (por ejemplo, metilsulfonilo, carboximetilsulfonilo);

(20) un grupo arilsulfonilo C_{6-14} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6}, un grupo carbonilo, un grupo carbamoilo, un grupo tiocarbamoilo, un grupo alcoxicarbonilo C_{1-6} y un grupo alquilsulfonilo C_{1-6} (por ejemplo, fenilsulfonilo; metilfenilsulfonilo; carboxifenilsulfonilo; metoxicarbonilfenilsulfonilo; metilsulfonilfenilsulfonilo);

(21) un grupo heterociclico conteniendo nitrógeno (por ejemplo, pirrolidinil, piperidinil, piperazinil, morfolin, oxopiperazinil)-carbonilo opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado de un grupo hidroxilo, un grupo alquilo C_{1-6} (el grupo alquilo C_{1-6} es opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo), un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo (por ejemplo, pirrolidinilcarbonilo, piperidinilcarbonilo, piperazinilcarbonilo, oxopiperazinilcarbonilo, morfolinocarbonilo, metoxicarbonilpirrolidinilcarbonilo);

(22) un grupo aril C_{6-14}-heterociclico conteniendo nitrógeno

(por ejemplo, pirrolidinil, piperidinil, piperazinil, morfolin)-carbonilo (por ejemplo, fenilpiperazinilcarbonilo, fenilpiperidinilcarbonilo) opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo);

(23) un grupo aralquil C_{7-13}-heterocíclico conteniendo nitrógeno (por ejemplo, pirrolidinil, piperidinil, piperazinil, morfolin)-carbonilo (por ejemplo, bencilpiperazinilcarbonilo) opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo);

(24) un grupo heterocíclico aromático (por ejemplo, piridil, tiazolil, oxazolil, indolil)-sulfonilo opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6} y un grupo mono- o di-(alquil C_{1-6}-carbonil)-amino (por ejemplo, 2-acetilamino-4-metil-5-tiazolilsulfonilo);

(25) un grupo heterocíclico no aromático (por ejemplo, oxodioxolil, oxodioxolanil, oxo-2-benzofuranil)oxi-carbonilo (por ejemplo, oxodioxolaniloxicarbonilo, oxo-2-benzofuraniloxicarbonilo);

(26) un grupo alquilsulfinilo C_{1-6} (por ejemplo, metilsulfinilo);

(27) un grupo tiocarbamoilo;

(28) un grupo fosfono opcionalmente mono- ó disustituido por un grupo alquilo C_{1-6} (por ejemplo, dimetil fosfono, dietil

fosfono);

(29) un grupo aralquil C_{7-13}-carbonilo (por ejemplo, bencilcarbonilo, fenetilcarbonilo);

(30) un grupo arilalquenil C_{8-13}-carbonilo (por ejemplo, estirilcarbonilo);

(31) un grupo heterocíclico aromático (por ejemplo, furil, tienil, oxazolil, tiazolil, isoxazolil, isotiazolil, pirazolil, piridil, pirazinil, benzofuril, benzotienil, quinoxalinil)-carbonilo (por ejemplo, furilcarbonilo, tienilcarbonilo, tiazolilcarbonilo, pirazolilcarbonilo, piridilcarbonilo, pirazinilcarbonilo, benzofurilcarbonilo, benzotienilcarbonilo, quinoxalinilcarbonilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6}, un grupo arilo C_{6-14}, un grupo aralquilo C_{7-13}, un grupo alcoxilo C_{1-6}, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(32) un grupo tetrahidropiranilcarbonilo;

(33) un grupo 4-oxo-4,5,6,7-tetrahidro-1-benzofuranil-carbonilo;

(34) un grupo cicloalquil C_{3-10}-alcoxicarbonilo C_{1-6} (por ejemplo, ciclohexilmetoxicarbonilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(35) un grupo heterocíclico aromático (por ejemplo, tienil,

furil, piridil, oxazolil, tiazolil, tetrazolil, piridil, quinolil, indolil)-aralquiloxi C_{7-13}-carbonilo (por ejemplo, tetrazolilbenciloxicarbonilo);

(36) un grupo heterocíclico aromático (por ejemplo, tienil, furil, piridil, tiazolil, oxazolil, indolil)-carbamoilo (por ejemplo, tienilcarbamoilo, furilcarbamoilo, tiazolilcarbamoilo, oxazolilcarbamoilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

y lo similar puede mencionarse.

El "grupo acilo" para X es preferentemente

(1) un grupo carbonilo;

(2) un grupo carbamoilo;

(3) un grupo alcoxicarbonilo C_{1-6} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo carbamoilo, un grupo tiocarbamoilo, un grupo alcoxicarbonilo C_{1-6} y un grupo alquil C_{1-6}-carboniloxilo (por ejemplo, metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, terc-butoxicarbonilo; carboximetoxicarbonilo, carboxietoxicarbonilo, carboxibutoxicarbonilo; carbamoilmetoxicarbonilo; tiocarbamoilometoxicarbonilo; etoxicarbonilmetoxicarbonilo, etoxicarboniletoxicarbonilo, metoxicarbonilbutoxicarbonilo, etoxicarbonilbutoxicarbonilo; terc-butilcarboniloximetoxicarbonilo);

(4) un grupo carbamoilo mono- o disustituido por un grupo alquilo C_{1-6} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un átomo halógeno y un grupo alcoxilo C_{1-6} (por ejemplo, metilcarbamoilo, etilcarbamoilo, dimetilcarbamoilo, dietilcarbamoilo, etilmetilcarbamoilo, propilcarbamoilo, isopropilcarbamoilo, butilcarbamoilo, isobutilcarbamoilo, trifluoroetilcarbamoilo, N-metoxietil-N-metilcarbamoilo);

(5) un grupo carbamoil-alquil C_{1-6}-carbamoilo opcionalmente mono- o disustituido por un grupo alquilo C_{1-6} opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, carbamoilmetilcarbamoilo, carbamoiletilcarbamoilo, dimetilcarbamoilmetilcarbamoilo, dimetilcarbamoiletilcarbamoilo);

y lo similar. De los mismos, es preferible un grupo carbonilo.

Como el "grupo hidroxilo sustituido" para X, por ejemplo, puede mencionarse un grupo hidroxilo sustituido por un sustituyente seleccionado de un grupo alquilo C_{1-10}, un grupo alquenilo C_{2-10}, un grupo cicloalquilo C_{3-10}, un grupo cicloalquenilo C_{3-10}, un grupo arilo C_{6-14}, un grupo aralquilo C_{7-13}, un grupo arilalquenilo C_{8-13}, un grupo alquil C_{1-6}-carbonilo (por ejemplo, acetilo, isobutanoilo, isopentanoilo), un grupo heterocíclico aromáticos de 5- o 6-miembros (por ejemplo, furilo, tienilo, tiazolilo,

oxazolilo, imidazolilo, triazolilo, pirazolilo, pirimidinilo), un grupo heterocíclico aromáticos fusionado (por ejemplo, indolilo) y lo similar, cada uno de los cuales es opcionalmente sustituido.

Como el grupo alquilo C_{1-10}, un grupo alquenilo C_{2-10}, un grupo cicloalquilo C_{3-10}, un grupo cicloalquenilo C_{3-10}, un grupo arilo C_{6-14}, un grupo aralquilo C_{7-13} y un grupo arilalquenilo C_{8-13} en la presente, pueden usarse los indicados a manera de ejemplo para "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para R^1 ó R^2 mencionados precedentemente.

El grupo alquilo C_{1-10} mencionado, grupo alquenilo C_{2-10}, grupo cicloalquilo C_{3-10}, grupo cicloalquenilo C_{3-10}, grupo arilo C_{6-14}, grupo aralquilo C_{7-13}, grupo arilalquenilo C_{8-13}, grupo alquil C_{1-6}-carbonilo, grupo heterocíclico aromático de 5- ó 6- miembros y grupos heterocíclico aromáticos fusionados cada uno opcionalmente posee 1 a 3 sustituyente(s) en posición(es) sustituible(s). Como estos sustituyentes, por ejemplo, puede mencionarse

un átomo halógeno (por ejemplo, flúor, cloro, bromo, iodo);

un grupo hidroxilo;

un grupo ciano;

un grupo alquilo C_{1-6} opcionalmente sustituido por 1 ó 2 sustituyente(s) seleccionado(s) de un átomo halógeno (por

ejemplo, flúor, cloro, bromo, iodo), un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} (por ejemplo, metoxicarbonilo, terc-butoxicarbonilo) y un grupo carbamoilo;

un grupo alcoxilo C_{1-6} opcionalmente sustituido por 1 ó 2 sustituyente(s) seleccionado de un átomo halógeno (por ejemplo, flúor, cloro, bromo, iodo), un grupo carbonilo y un grupo alcoxicarbonilo C_{1-6} (por ejemplo, terc-butoxicarbonilo);

un grupo alquiltio C_{1-6} (por ejemplo, metiltio, etiltio);

un grupo alquil C_{1-6}-carbonilo;

un grupo carboxilo;

un grupo alcoxicarbonilo C_{1-6} (por ejemplo, metoxicarbonilo, etoxicarbonilo);

un grupo carbamoilo opcionalmente mono- o di-sustituido por un grupo alquilo C_{1-10} (por ejemplo, metilo, etilo, propilo, isopropilo, neopentilo);

un grupo amino opcionalmente mono- o disustituido por un grupo alquilo C_{1-10} (por ejemplo, metilo, etilo, propilo, isopropilo, neopentilo);

un grupo alquil C_{1-6}-carbonilamino;

un grupo heterocíclico aromático (por ejemplo, furilo, tienilo, oxazolilo, tiazolilo, isoxazolilo, tetrazolilo, oxadiazolilo, tiadiazolilo, piridilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6} (por ejemplo, metilo, etilo), grupo

carboxilo, un grupo alcoxicarbonilo C_{1-6} (por ejemplo, metoxicarbonilo, etoxicarbonilo) y un grupo carbamoilo;

un grupo alquilsulfinilo C_{1-6} (por ejemplo, metilsulfinilo);

un grupo alquilsulfonilo C_{1-6} (por ejemplo, metilsulfonilo);

y lo similar.

Como los ejemplos preferibles del "grupo hidroxilo sustituido", puede mencionarse

(1) un grupo alquil C_{1-6}-carboniloxilo;

(2) un grupo alcoxilo C_{1-10} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo hidróxilo, un grupo carbonilo, un grupo carbamoilo y un grupo alcoxicarbonilo C_{1-6};

(3) un grupo ariloxilo C_{6-14} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un átomo halógeno, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6}, un grupo alquiltio C_{1-6}, un grupo carbamoilo, un grupo alcoxilo C_{1-6}, un grupo alquilsulfonilo C_{1-6}, un grupo alquilsulfinilo C_{1-6} y un grupo alquilo C_{1-6} (el grupo alquilo C_{1-6} es opcionalmente sustituido por 1 ó 2 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo Cs6 y un grupo carbamoilo);

(4) un grupo heterocicliloxilo aromático de 5- ó 6- miembros (preferentemente tieniloxilo, tiazoliloxilo, oxazoliloxilo,

imidazoliloxilo, triazoliloxilo, pirazoliloxilo, piridiloxilo, pirimidiniloxilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado de un grupo alquilo C_{1-6} (el grupo alquilo C_{1-6} es opcionalmente sustituido por 1 a 2 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo), un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(5) un grupo heterocicliloxilo aromático funsionado (preferentemente indoliloxilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(6) un grupo heterocíclico aromático (preferentemente piridil)- alcoxilo C_{1-6} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(7) un grupo heterocíclico aromático (preferentemente tetrazolil)-ariloxilo C_{6-14};

y lo similar.

Como el "grupo tiol opcionalmente sustituido" para X, por ejemplo, puede mencionarse un grupo tiol opcionalmente sustituido por un sustituyente seleccionado de un grupo alquilo C_{1-10}, un grupo alquenilo C_{2-10}, un grupo cicloalquilo C_{3-10}, un grupo cicloalquenilo C_{3-10}, un grupo arilo C_{6-14}, un grupo aralquilo C_{7-13}, un grupo arilalquenilo C_{8-13}, un grupo

alquil C_{1-6}-carbonilo (por ejemplo, acetilo, isobutanoilo, isopentanoilo), un grupo heterocíclico aromático de 5- ó 6-miembros (por ejemplo, furilo, tienilo, tiazolilo, oxazolilo, imidazolilo, triazolilo, pirazolilo, pirimidinilo), un grupo heterocíclico aromáticos fusionado (por ejemplo, indolilo) y lo similar cada uno de los cuales es opcionalmente sustituido.

Como el grupo alquilo C_{1-10}, pueden usarse grupo alquenilo C_{2-10}, grupo cicloalquilo C_{3-10}, grupo cicloalquenilo C_{3-10}, grupo arilo C_{6-14}, grupo aralquilo C_{7-13} y grupo arilalquenilo C_{8-13} en la presente, los indicados a manera de ejemplo para "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" mencionado para el R^1 ó R2.

El mencionado grupo alquilo C_{1-10}, grupo alquenilo C_{2-10}, grupo cicloalquilo C_{3-10}, grupo cicloalquenilo C_{3-10}, grupo arilo C_{6-14}, grupo aralquilo C_{7-13}, grupo arilalquenilo C_{8-13}, grupo alquil C_{1-6}-carbonilo, grupo heterocíclico aromático de 5- ó 6- miembros y grupo heterocíclico aromático fusionado cada uno opcionalmente posee 1 a 3 sustituyente(s) en posición(es) sustituible(s). Como éstos sustituyentes, pueden usarse sustituyentes para grupo alquilo C_{1-10} y lo similar para el "grupo hidroxilo sustituido" para X mencionado.

Como los ejemplos preferibles de "grupo tiol opcionalmente sustituido", pueden mencionarse

(1) un grupo alquiltio C_{1-6} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de grupo hidroxilo, un grupo carbonilo, un grupo carbamoilo y grupo alcoxicarbonilo C_{1-6};

(2) un grupo ariltio C_{6-14} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6}, un grupo alquiltio C_{1-6} y un grupo carbamoilo;

(3) un grupo heterociclíltio aromático de 5 ó 6 miembros (preferentemente tieniltio, tiazoliltio, oxazoliltio, imidazoliltio, triazoliltio, pirazoliltio, piridiltio, pirimidiniltio) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6}, un grupo carbonilo, un grupo alcoxicarbonilo C1-6 y un grupo carbamoilo;

y lo similar.

Como el "grupo amino opcionalmente sustituido" para X, pueden usarse aquéllos indicados a manera de ejemplo para el R^4 mencionado.

Como el "grupo cíclico" del "grupo cíclico opcionalmente sustituido" para X, por ejemplo, puede mencionarse un grupo hidrocarburo aromático, un grupo hidrocarburo cíclico no aromático, un grupo heterocíclico aromático, un grupo heterocíclico no aromático y lo similar.

Como el grupo hidrocarburo aromático y el grupo heterocíclico aromático, pueden usarse aquéllos indicados a

manera de ejemplo para el "grupo aromático" del "grupo aromático opcionalmente sustituido" para el R^3 mencionado.

Adicionalmente, como el grupo heterocíclico no aromático, pueden usarse aquéllos indicados a manera de ejemplo para el "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para el R^5 mencionado.

Como el grupo hidrocarburo cíclico no aromático, por ejemplo, puede mencionarse un grupo cicloalquilo C_{3-10}, un grupo cicloalquenilo C_{3-10}, un grupo cicloalcadienilo C_{4-10} y lo similar, cada uno de los cuales es opcionalmente fusionado con un anillo de benceno.

Como grupo cicloalquilo C_{3-10}, grupo cicloalquenilo C_{3-10} y grupo cicloalcadienilo C_{4-10} en la presente, pueden usarse aquéllos indicados a manera de ejemplo para el "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para el R^1 o R^2 mencionado precedentemente.

El "grupo cíclico" del "grupo cíclico opcionalmente sustituido" para X posee opcionalmente 1 a 3 sustituyente(s) en posición(es) sustituible(s).

Como estos sustituyentes, por ejemplo, pueden mencionarse aquéllos indicados a manera de ejemplo para sustituyentes para grupo cicloalquilo C_{3-10} indicado para el "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para el R^1 ó R^2 mencionado a manera de ejemplo.

Los sustituyentes son preferentemente

un grupo alquilo C_{1-6} (por ejemplo, metilo, etilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un átomo halógeno (por ejemplo, flúor, cloro, bromo, iodo), un grupo carbamoilo, un grupo carbonilo y un grupo alcoxicarbonilo C_{1-6} (por ejemplo, metoxicarbonilo, etoxicarbonilo);

un átomo halógeno (por ejemplo, flúor, cloro, bromo, iodo);

un grupo carboxilo;

un grupo alcoxicarbonilo C_{1-6};

un grupo carbamoilo;

y lo similar.

El X es preferentemente un grupo acilo, un grupo hidroxilo sustituido, un grupo tiol opcionalmente sustituido o un grupo amino opcionalmente sustituido, más preferentemente un grupo acilo. De los mismos,

(1) un grupo carbonilo;

(2) un grupo carbamoilo;

(3) un grupo alcoxicarbonilo C_{1-6} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo carbamoilo, un grupo tiocarbamoilo, un grupo alcoxicarbonilo C_{1-6} y un grupo alquil C_{1-6}-carboniloxilo;

(4) un grupo carbamoilo mono- o disustituido opcionalmente por un grupo alquilo C_{1-6} sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un átomo halógeno y un grupo alcoxilo C_{1-6};

(5) un grupo carbamoil-alquil C_{1-6}-carbamoilo opcionalmente mono- o disustituido opcionalmente por un grupo alquilo C_{1-6} sustituido por 1 a 3 átomo(s) halógenos;

y lo similar es preferible, y un grupo carbonilo es particularmente preferible.

Del compuesto (I), cuando el X es un grupo etoxicarbonilo, entonces Q es un grupo de hidrocarburo de cadena bivalente.

Además, el compuesto (I) no comprende

2,6-diisopropil-3-metilaminometil-4-(4-fluorofenil)-5-pentilpiridina [este compuesto también se designa como {[4-(4-fluorofenil)-2,6-diisopropil-5-pentilpiridin-3-il]metil}metilamina];

2,6-diisopropil-3-aminometil-4-(4-fluorofenil)-5-pentilpiridina [este compuesto también se designa como {[4-(4-fluorofenil)-2,6-diisopropil-5-pentilpiridin-3-il]metil}amina];

2,6-diisopropil-3-(dimetilamino)metil-4-(4-fluorofenil)-5-pentilpiridina [este compuesto también se designa como 1-[4-(4-fluorofenil)-2,6-diisopropil-5-pentilpiridin-3-il]-N,N-dimetilmetanamina];

2,6-diisopropil-3-(etilamino)metil-4-(4-fluorofenil)-5-pentilpiridina [este compuesto también se designa como N-{[4-(4-fluorofenil)-2,6-diisopropil-5-pentilpiridin-3-il]metil}etanamina]; y

3-(terc-butildimetilsililoximetil)-2,6-diisopropil-4-(4-fluorofenil)-5-(indolil-5-aminometil)piridina [este compuesto también se designa como N-{[5-({[terc-butil(dimetil)silil]oxi}metil)-4-(4-fluorofenil)-2,6-diisopropilpiridin-3-il]metil}-1H-indol-5-amina].

Como los ejemplos preferibles de compuesto (I), pueden mencionarse los compuestos siguientes.

[Compuesto A]

Un compuesto en donde

R^1 y R^2 son iguales o diferentes y cada uno es un grupo alquilo C_{1-10} (preferentemente metilo, etilo, propilo, isopropilo, butilo, isobutilo, neopentilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo cicloalquilo C_{3-10} (preferentemente ciclopropilo), grupo alcoxicarbonilo C_{1-6} (preferentemente metoxicarbonilo) y lo similar;

R^3 es un grupo arilo C_{6-14} (el grupo arilo C_{6-14} es preferentemente fenilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6} (por ejemplo, metilo, etilo) opcionalmente sustituido por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo), un átomo halógeno (por ejemplo, flúor, cloro, bromo, iodo) y lo similar;

R^4 es opcionalmente un grupo amino mono- o disustituido por un grupo alquilo C_{1-6} (por ejemplo, metilo, etilo,

propilo, isopropilo);

L es un grupo alquileno C_{1-10} (preferentemente $-CH_2-$);

Q es un enlace, un grupo alquileno C_{1-10} o un grupo alquenileno C_{2-10} (preferentemente un enlace, $-CH_2-$, $-(CH_2)_2-$, $-CH=CH-$); y

X es un grupo carbonilo;

un grupo carbamoilo;

un grupo alcoxicarbonilo C_{1-6};

un grupo carbamoilo mono- o disustituido opcionalmente por un grupo alquilo C_{1-6} sustituido por 1 a 3 átomo(s) halógenos; o

un grupo carbamoil-alquil C_{1-6}-carbamoilo opcionalmente mono- o disustituido opcionalmente por un grupo alquilo C_{1-6} sustituido por 1 a 3 átomo(s) halógenos.

[Compuesto B]

Un compuesto en donde

R^1 y R^2 son iguales o diferentes y cada uno es

(1) un grupo alquilo C_{1-10} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo cicloalquilo C_{3-10} (preferentemente ciclopropilo), un grupo alcoxicarbonilo C_{1-6}, un grupo alcoxilo C_{1-6} y lo similar;

(2) un grupo arilo C_{6-14} (preferentemente fenilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un átomo halógeno, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6}, un grupo carbamoilo y lo similar; o

(3) un grupo aralquilo C_{7-13} (preferentemente bencilo);

R^3 es un grupo arilo C_{6-14} (el grupo arilo C_{6-14} es preferentemente fenilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) opcionalmente de un grupo alquilo C_{1-6} sustituido por 1 a 3 átomo(s) halógenos, un átomo halógeno, un grupo alcoxicarbonilo C_{1-6}, un grupo carbonilo, un grupo hidroxilo, un grupo alcoxilo C_{1-6} opcionalmente sustituido por 1 a 3 átomo(s) halógenos, y lo similar;

R^4 es un grupo amino opcionalmente mono- o disustituido por un grupo alquilo C_{1-6} (preferentemente un grupo amino);

L es un grupo alquileno C_{1-10} (preferentemente $-CH_2-$);

Q es un enlace, un grupo alquileno C_{1-10} o un grupo alquenileno C_{2-10} (preferentemente un enlace, $-CH_2-$, $-(CH_2)_2-$, $-CH=CH-$); y

X es

(1) un átomo de hidrógeno;

(2) un grupo ciano;

(3) (3a) un grupo carbonilo;

(3b) un grupo carbamoilo;

(3c) un grupo alcoxicarbonilo C_{1-6} opcionalmente sustituido por sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo carbamoilo, un grupo tiocarbamoilo, un grupo alcoxicarbonilo C_{1-6} y un grupo alquil C_{1-6}-carboniloxilo;

(3d) un grupo heterocíclico aromático (preferentemente

piridil, tiazolil, oxazolil, indolil)-alcoxi C_{1-6}-carbonilo opcionalmente sustituido por sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo carbamoilo, un grupo tiocarbamoilo y un grupo alcoxicarbonilo C_{1-6};

(3e) un grupo heterocíclico no aromático (preferentemente oxodioxolil, oxodioxolanil, oxo-2-benzofuranil)-alcoxi C_{1-6}-carbonilo opcionalmente sustituido por un grupo alquilo C_{1-6};

(3f) un grupo aralquiloxi-C_{7-13}-carbonilo opcionalmente sustituido por sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo carbamoilo, un grupo tiocarbamoilo y un grupo alcoxicarbonilo C_{1-6};

(3g) un grupo carbamoilo opcionalmente mono- o disustituido por un grupo alquilo C_{1-6} sustituido por sustituyente(s) seleccionado(s) de 1 a 3 átomo(s) halógenos y un grupo alcoxilo C_{1-6};

(3h) un grupo carbamoil-alquil C_{1-6}-carbamoilo opcionalmente mono- o disustituido por un grupo alquilo C_{1-6} opcionalmente sustituido por 1 a 3 átomo(s) halógenos;

(3i) un grupo alcoxi C_{1-6}-carbonil-alquil C_{1-6}-carbamoilo opcionalmente sustituido por un grupo alquilo C_{1-6};

(3j) un grupo mono- o dicicloalquil C_{3-10}-carbamoilo opcionalmente sustituido por un grupo alquilo C_{1-6};

(3k) un grupo aralquil C_{7-13}-carbamoilo opcionalmente sustituido por sustituyente(s) seleccionado(s) de un átomo

halógeno, un grupo hidroxilo, un grupo alcoxicarbonilo C_{1-6} y un grupo alquilo C_{1-6};

(3l) un grupo heterocíclico aromático (preferentemente piridil, tiazolil, oxazolil, indolil)-alquil C_{1-6}-carbamoilo;

(3m) un grupo alquilsulfonilo C_{1-6} opcionalmente sustituido por sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo carbamoilo y grupo alcoxicarbonilo C_{1-6};

(3n) un grupo arilsulfonilo C_{6-14} opcionalmente sustituido por sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6}, un grupo carbonilo, un grupo carbamoilo, un grupo tiocarbamoilo, un grupo alcoxicarbonilo C_{1-6} y un grupo alquilsulfonilo C_{1-6};

(3o) un grupo heterocíclico conteniendo nitrógeno (preferentemente pirrolidinil, piperidin, piperazinil, morfolino)-carbonilo opcionalmente sustituido por sustituyente(s) seleccionado(s) de un grupo hidroxilo y un grupo alcoxicarbonilo C_{1-6};

(3p) un grupo aril C_{6-14}-heterocíclico conteniendo nitrógeno (preferentemente pirrolidinil, piperidino, piperazinil, morfolino)-carbonilo opcionalmente sustituido por un átomo halógeno;

(3q) un grupo aralquil C_{7-13}-heterocíclico conteniendo nitrógeno (preferentemente pirrolidinil, piperidino, piperazinil, morfolino)-carbonilo opcionalmente sustituido por un átomo halógeno;

(3r) un grupo heterocíclico no aromático (preferentemente oxodioxolil, oxodioxolanil, oxo-2-benzofuranil)oxi-carbonilo; o

(3s) un grupo fosfono opcionalmente mono- o di-sustituido por un grupo alquilo C_{1-6};

(4) un grupo alquil C_{1-6}-carboniloxilo;

(5) (5a) un grupo alquiltio C_{1-6} opcionalmente sustituido por sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo carbamoilo y un grupo alcoxicarbonilo C_{1-6};

(5b) un grupo ariltio C_{6-14} (preferentemente feniltio) opcionalmente sustituido por sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo alquiltio C_{1-6}; o

(5c) un grupo heterocicliltio aromático de 5 miembros (preferentemente tiazoliltio, oxazoliltio, triazoliltio) opcionalmente sustituido por un grupo alquilo C_{1-6};

(6) (6a) un grupo amino;

(6b) un grupo alcoxi C_{1-6}-carbonil-alquilamino C_{1-10} (preferentemente metoxicarbonilmetilamino, etoxicarbonilmetilamino, terc-butoxicarbonilmetilamino);

(6c) un grupo carboxi-alquilamino C_{1-10};

(6d) un grupo aralquiloxi C_{7-13}-carbonilamino;

(6e) un grupo carbamoiloamino;

(6f) un grupo mono- o dialquil C1-6-carbamoiloamino;

(6g) un grupo alquilsulfonilamino C_{1-6};

(6h) un grupo arilsulfonilamino C_{6-14} opcionalmente sustituido por un grupo alquilsulfonilo C_{1-6}; o

(6i) un grupo heterocíclico aromático (por ejemplo, piridil, tiazolil, oxazolil, indolil)-sulfonilamino opcionalmente sustituido por sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6} y un grupo mono- o di-(alquil C_{1-6}-carbonil)-amino; o

(7) tetrazolilo, oxoimidazolidinilo (preferentemente 2-oxoimidazolidin-1-ilo), dioxoimidazolidinilo (preferentemente 2,4-dioxoimidazolidin-3-ilo), oxopiperazinilo (preferentemente 3-oxopiperazin-1-ilo), dioxopiperazinilo (preferentemente 2,3-dioxopiperazin-1-ilo, 2,5-dioxopiperazin-1-ilo) u oxodihidrooxadiazolilo (preferentemente 5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-ilo).

[Compuesto C]

Un compuesto en donde R^4 es un grupo amino, y X es cualquiera de los mencionados precedentemente (3a)-(3s) en el Compuesto B mencionado precedentemente.

[Compuesto D]

Un compuesto en donde

R^1, R^2, R^3, R^4, L y Q son iguales a los definidoa para el Compuesto B mencionado precedentemente, X es

(1) un átomo de hidrógeno;

(2) un grupo ciano;

(3) (3a) un grupo carbonilo;

(3b) un grupo carbamoilo;

(3c) un grupo alcoxicarbonilo C_{1-6} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo carbamoilo, un grupo tiocarbamoilo, un grupo alcoxicarbonilo C_{1-6} y un grupo alquil C_{1-6}-carboniloxilo;

(3d) un grupo heterocíclico aromático (preferentemente furil, tienil, piridil, tiazolil, oxazolil, pirazinil, indolil)-alcoxi C_{1-6}-carbonilo opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo carbamoilo, un grupo tiocarbamoilo y un grupo alcoxicarbonilo C_{1-6};

(3e) un grupo heterocíclico no aromático (preferentemente oxodioxolil, oxodioxolanil, oxo-2-benzofuranil)-alcoxi C_{1-6}-carbonilo opcionalmente sustituido por un grupo alquilo C_{1-6};

(3f) un grupo aralquiloxi C_{7-13}-carbonilo opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo carbamoilo, un grupo tiocarbamoilo, un grupo alcoxicarbonilo C_{1-6}, un átomo halógeno, un grupo ciano, un grupo nitro, un grupo alcoxilo C_{1-6}, un grupo alquilsulfonilo C_{1-6} y un grupo alquilo C_{1-6} (el grupo alquilo C_{1-6} es opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un átomo halógeno, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo);

(3g) un grupo carbamoilo mono- o disustituido por un grupo alquilo C_{1-6} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un átomo halógeno y un grupo alcoxilo C_{1-6};

(3h) un grupo carbamoil-alquil C_{1-6}-carbamoilo opcionalmente mono- o disustituido por un grupo alquilo C_{1-6} opcionalmente sustituido por 1 a 3 átomo(s) halógenos;

(3i) un grupo alcoxi C_{1-6}-carbonil-alquil C_{1-6}-carbamoilo opcionalmente sustituido por un grupo alquilo C_{1-6};

(3j) un grupo mono- o dicicloalquil C_{3-10}-carbamoilo opcionalmente sustituido por un grupo alquilo C_{1-6};

(3k) un grupo aralquil C_{7-13}-carbamoilo opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un átomo halógeno, un grupo hidroxilo, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo alquilo C_{1-6};

(3l) un grupo heterocíclico aromático (preferentemente piridil, tienil, furil, tiazolil, oxazolil, indolil)-alquil C_{1-6}-carbamoilo opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo carbamoilo y un grupo alcoxicarbonilo C_{1-6};

(3m) un grupo alquilsulfonilo C_{1-6} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo carbamoilo y un grupo alcoxicarbonilo C_{1-6};

(3n) un grupo arilsulfonilo C_{6-14} opcionalmente sustituido

por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6}, un grupo carbonilo, un grupo carbamoilo, un grupo tiocarbamoilo, un grupo alcoxicarbonilo C_{1-6} y un grupo alquilsulfonilo C_{1-6};

(3o) un grupo heterocíclico conteniendo nitrógeno (preferentemente pirrolidinil, piperidinil, piperazinil, morfolino)-carbonilo opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo hidroxilo, un grupo carbonilo y un grupo alcoxicarbonilo C_{1-6};

(3p) un grupo aril C_{6-14}-heterocíclico conteniendo nitrógeno (preferentemente pirrolidinil, piperidinil, piperazinil, morfolino)-carbonilo opcionalmente sustituido por 1 a 3 átomo(s) halógenos;

(3q) un grupo aralquil C_{7-13}-heterocíclico conteniendo nitrógeno (preferentemente pirrolidinil, piperidinil, piperazinil, morfolino)-carbonilo opcionalmente sustituido por 1 a 3 átomo(s) halógenos;

(3r) un grupo heterocíclico no aromático (preferentemente oxodioxolil, oxodioxolanil, oxo-2-benzofuranil)oxi-carbonilo;

(3s) un grupo fosfono opcionalmente mono- o disustituido por un grupo alquilo C_{1-6};

(3t) un grupo heterocíclico aromático (preferentemente tetrazoili)-aralquiloxi C_{7-13}-carbonilo;

(3u) un grupo cicloalquil C_{3-10}-alcoxicarbonilo C_{1-6}

opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(3v) un grupo aril C_{6-14}-carbamoilo opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado opcionalmente de un grupo amino mono- o disustituido por un grupo alquilo C_{1-6}, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6}, un grupo heterocíclico aromático (preferentemente tetrazolilo, oxadiazolilo), un grupo heterocíclico no aromático (preferentemente oxooxadiazolilo) y un grupo carbamoilo; o

(3w) un grupo heterocíclico aromático (preferentemente tienil, furil)-carbamoilo opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(4) (4a) un grupo alquil C_{1-6}-carboniloxilo;

(4b) un grupo alcoxilo C_{1-10} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo hidroxilo, un grupo carbonilo, un grupo carbamoilo y un grupo alcoxicarbonilo C_{1-6};

(4c) un grupo ariloxilo C_{6-14} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un átomo halógeno, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6}, un grupo alquiltio C_{1-6}, un grupo carbamoilo, un grupo alcoxilo C_{1-6}, un grupo alquilsulfonilo C_{1-6}, un grupo alquilsulfinilo C_{1-6} y un

grupo alquilo C_{1-6} (el grupo alquilo C_{1-6} es opcionalmente sustituido por 1 o 2 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo);

(4d) un grupo heterocicliloxilo aromático de 5- ó 6-miembros (preferentemente tieniloxilo, tiazoliloxilo, oxazoliloxilo, imidazoliloxilo, triazoliloxilo, pirazoliloxilo, piridiloxilo, pirimidiniloxilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6} (el grupo alquilo C_{1-6} es opcionalmente sustituido por 1 o 2 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo), un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(4e) un grupo heterocicliloxilo aromático fundido (preferentemente indoliloxilo) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(4f) un grupo heterocíclico aromático (preferentemente piridil)-alcoxilo C_{1-6} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo; o

(4g) un grupo heterocíclico aromático (preferentemente tetrazolil)-ariloxilo C_{6-14};

(5) (5a) un grupo alquiltio C_{1-6} opcionalmente sustituido por

1 a 3 sustituyente(s) seleccionado(s) de un grupo hidroxilo, un grupo carbonilo, un grupo carbamoilo y un grupo alcoxicarbonilo C_{1-6};

(5b) un grupo ariltio C_{6-14} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6}, un grupo alquiltio C_{1-6} y un grupo carbamoilo; o

(5c) un grupo heterociclíltio aromático de 5- ó 6-miembros (preferentemente tieniltio, tiazoliltio, oxazoliltio, imidazoliltio, triazoliltio, pirazoliltio, piridiltio, pirimidiniltio) opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6}, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(6) (6a) un grupo amino;

(6b) un grupo alcoxi C_{1-6}-carbonil-alquilamino C_{1-10};

(6c) un grupo carboxi-alquilamino C_{1-10};

(6d) un grupo aralquiloxi C_{7-13}-carbonilamino opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(6e) un grupo carbamoiloamino;

(6f) un grupo mono- o dialquil C_{1-6}-carbamoiloamino;

(6g) un grupo alquilsulfonilamino C_{1-6};

(6h) un grupo arilsulfonilamino C_{6-14} opcionalmente

sustituido por un grupo alquilsulfonilo C1-6;

(6i) un grupo heterocíclico aromático (por ejemplo, piridil, tiazolil, oxazolil, indolil)-sulfonilamino opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo de alquilo C_{1-6} y un grupo mono - o di-(alquil C_{1-6}-carbonil)-amino;

(6j) un grupo mono - o di-(alquil C_{1-6}-carbonil)-amino;

(6k) un grupo cicloalquil C_{3-10}-carbonilamino;

(6l) un grupo aril C6-14-carbonilamino opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un átomo halógeno, un grupo ciano, un grupo alquilo C_{1-6} opcionalmente halogenado, un grupo alcoxilo C_{1-6}, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6}, un grupo heterocíclico aromático (preferentemente tetrazolilo, oxadiazolilo), un grupo heterocíclico no aromático (preferentemente oxooxadiazolilo) y un grupo carbamoilo;

(6m) un grupo aralquil C_{7-13}-carbonilamino;

(6n) un grupo arilalquenil C_{8-13}-carbonilamino;

(6o) un grupo heterocíclico aromático (preferentemente furil, tienil, oxazolil, tiazolil, isoxazolil, isotiazolil, pirazolil, piridil, pirazinil, benzofuril, benzotienil, quinoxalinil)-carbonilamino opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6}, un grupo arilo C_{6-14}, un grupo aralquilo C_{7-13}, un grupo alcoxilo C_{1-6}, un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un

grupo carbamoilo;

(6p) un grupo heterocíclico conteniendo nitrógeno (preferentemente pirrolidinil, piperidinil, piperazinil, morfolino)-carbonilamino opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6} (el grupo alquilo C_{1-6} es opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo), un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(6q) un grupo aril C_{6-14}-heterocíclico conteniendo nitrógeno (por ejemplo, pirrolidinilo, piperidinilo, piperazinilo, morfolino)-carbonilamino;

(6r) un grupo tetrahidropiranilcarbonilamino;

(6s) un grupo 4-oxo-4,5,6,7-tetrahidro-1-benzofuranil-carbonilamino;

(6t) un grupo alcoxicarbonilamino C_{1-6} opcionalmente sustituido por un grupo alcoxicarbonilo C_{1-6};

(6u) un grupo ariloxicarbonilamino C_{6-14} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo;

(6v) un grupo aralquilcarbamoiloamino C_{7-13}; o

(6w) un grupo heterocíclico aromático (preferentemente tiazolil, oxazolil)-carbamoiloamino opcionalmente sustituido

por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo, un grupo alcoxicarbonilo C_{1-6} y un grupo carbamoilo; o

(7) (7a) tetrazolilo;

(7b) oxoimidazolidinilo (preferentemente 2-oxoimidazolidin-1-ilo);

(7c) dioxoimidazolidinilo (preferentemente 2,4-dioxoimidazolidin-3-ilo, 2,4-dioxoimidazolidin-1-ilo) opcionalmente sustituido por un grupo alquilo C_{1-6} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo y un grupo alcoxicarbonilo C_{1-6};

(7d) oxopiperazinilo (preferentemente 3-oxopiperazin-1-ilo);

(7e) dioxopiperazinilo (preferentemente 2,3-dioxopiperazin-1-ilo, 2,5-dioxopiperazin-1-ilo);

(7f) oxodihidrooxadiazolilo (preferentemente 5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-ilo);

(7g) dioxoisoindolilo;

(7h) un grupo oxazolilo opcionalmente sustituido por un alcoxicarbonilo C_{1-6};

(7i) dioxooxazolidinilo (preferentemente 2,4-dioxooxazolidin-5-ilo) o dioxotiazolidinilo (preferentemente 2,4-dioxotiazolidin-5-ilo) cada uno de los cuales es opcionalmente sustituido por un grupo alquilo C_{1-6}

opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado de un grupo carbonilo y un grupo alcoxicarbonilo C_{1-6};

(7j) 4-oxo-2-tioxo-1,3-tiazolidin-5-ilo o 4-oxo-2-tioxo-1,3-oxazolidin-5-ilo cada uno de los cuales es opcionalmente sustituido por un grupo alquilo C_{1-6} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo carbonilo y un grupo alcoxicarbonilo C_{1-6};

(7k) 1,3(2H,5H)-dioxo-tetrahidroimidazo[1,5-a]piridinilo;

(7l) 1,3(2H,5H)-dioxo-10,10a-dihidroimidazo[1,5-b]isoquinolinilo; o

(7m) un grupo arilo C_{6-14} opcionalmente sustituido por un grupo alcoxicarbonilo C_{1-6}.

[Compuesto E]

El Compuesto D mencionado prececentemente en donde

R^1 y R^2 son iguales o diferentes y cada uno es un grupo alquilo C_{1-10} (preferentemente R^1 es isobutilo o neopentilo;

R^2 es metilo);

R^3 es un grupo arilo C_{6-14} opcionalmente sustituido por un grupo alquilo C_{1-6} (R^3 es preferentemente 4-metilfenilo);

R^4 es un grupo amino; y

X es el mencionado precedentemente (3a), (3c), (3f), (3o), (3v), (4d), (5b), (6l) o (6o) [preferiblemente (3a), (3o), (3v), (4d) o (6o)].

[Compuesto F]

Ácido 5-(Aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (Ejemplo 22);

Ácido 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (Ejemplo 40);

Metil 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxilato (Ejemplo 305);

{[2-isobutil-6-metil-4-(4-metilfenil)-5-(2-morfolin-4-il-2-oxoetil)pyridin-3-il]metil}amina (Ejemplo 312);

Metil 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoato (Ejemplo 336);

N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]isoxazol-4-carboxamida (Ejemplo 350); o una sal del mismo (preferentemente clorhidrato, trifluoroacetato, fumarato).

Como una sal del compuesto (I), es preferible una sal farmacológicamente aceptable. Los ejemplos de tal sal incluyen las sales con bases inorgánicas, las sales con bases orgánicas, sales con ácidos inorgánicos, sales con ácidos orgánicos, sales con aminoácidos básicos o ácidos y lo similar.

Los ejemplos preferibles de la sal con base inorgánica incluyen las sales del metal alcalino tal como la sal de sodio, sal de potasio y lo similar; sal de metal alcalino-

térreo tal como la sal de calcio, sal del magnesio y lo similar; sal de aluminio; la sal de amonio y lo similar.

Los ejemplos preferibles de la sal con base orgánica incluyen una sal con trimetilamina, trietilamina, piridina, picolina, etanolamina, dietanolamina, trietanolamina, trometamina[tris(hidroximetil)metilamina], terc-butilamina, ciclohexilamina, bencilamina, diciclohexilamina, N,N-dibenciletilendiamina y lo similar.

Los ejemplos preferibles de la sal con ácido inorgánico incluyen una sal con ácido clorhídrico, ácido bromhídrico, ácido nítrico, ácido sulfúrico, ácido fosfórico y lo similar.

Los ejemplos preferibles de la sal con ácido orgánico incluyen una sal con ácido fórmico, ácido acético, ácido ftálico, ácido trifluoracético, ácido fumárico, ácido oxálico, ácido tartárico, ácido maléico, ácido cítrico, ácido succínico, ácido málico, ácido metansulfónico, ácido bencensulfónico, ácido p-toluensulfónico y lo similar.

Los ejemplos preferibles de la sal con aminoácido básico incluyen una sal con arginina, lisina, ornitina y lo similar. Los ejemplos preferibles de la sal con aminoácido ácido incluyen una sal con ácido aspártico, ácido glutámico y lo similar.

De las sales indicadas precedentemente, es preferible la sal con ácido inorgánico y la sal con ácido orgánico, clorhidrato, trifluoroacetato, fumarato y lo similar es más

preferible.

Una prodroga del compuesto (I) es un compuesto que se convierte al compuesto (I) debido a la reacción por enzima, ácido gástrico y lo similar bajo condiciones fisiológicas en el cuerpo; es decir, un compuesto que se convierte al compuesto (I) por oxidación enzimática, reducción, hidrólisis y lo similar, y un compuesto que se convierte al compuesto (I) por hidrólisis y lo similar por medio del ácido gástrico y lo similar. Los ejemplos de una prodroga del compuesto (I) incluyen un compuesto en donde un grupo amino del compuesto (I) es acilado, alquilado, fosforilado (por ejemplo, un compuesto en donde el grupo amino del compuesto (I) es eicosanoilado, alanilado, pentilaminocarbonilado, (5-metil-2-oxo-1,3-dioxolen-4-il)metoxicarbonilado, tetrahidrofuranilado, pirrolidilmetilado, pivaloiloximetilado, terc-butilado y lo similar); un compuesto en donde un grupo hidroxilo del compuesto (I) es acilado, alquilado, fosforilado, boratado (por ejemplo, un compuesto dónde un grupo hidroxilo del compuesto (I) es acetilado, palmitoilado, propanoilado, pivaloilado, succinilado, fumarilado, alanilado, dimetilaminometilcarbonilado y lo similar); un compuesto en donde un grupo carbonilo de compuesto (I) es esterificado o amidado (por ejemplo, un compuesto en donde un grupo carbonilo del compuesto (I) es etilo esterificado, fenilo

esterificado, carboximetilo esterificado, dimetilaminometilo esterificado, pivaloiloximetilo esterificado, etoxicarboniloxietilo esterificado, ftalidilo esterificado, (5-metil-2-oxo-1,3-dioxolen-4-il)metilo esterificado, ciclohexiloxicarboniletilo esterificado, metilamidado y lo similar) y lo similar. Estos compuestos pueden producirse desde el compuesto (I) por un método conocido por se.

Una prodroga del compuesto (I) puede ser un compuesto que es convertido en el compuesto (I) bajo condiciones fisiológicas tal como las descriptas en "Development of Pharmaceutical Products", vol. 7, "Molecule Design", 163-198, Hirokawa Shoten (1990).

El compuesto (I) puede ser etiquetado con un isótopo (por ejemplo, ^{3}H, ^{14}C, ^{35}S, ^{125}I y lo similar) y lo similar.

El compuesto (I) puede ser un anhidrido o un hidrato.

El compuesto (I) y una prodroga del mismo (más adelante a veces simplemente denominado compuesto de la presente invención) presente una baja toxicidad y puede ser usado como un agente para profilaxis o tratamiento de varias enfermedades a ser mencionadas más adelante para mamíferos (por ejemplo, ser humano, ratón, rata, conejo, perro, gato, ganado, caballo, cerdo, simio y lo similar) los mismos son mezclados con un portador farmacológicamente aceptable y lo similar para dar una composición farmacéutica.

En la presente, varios portadores orgánicos o

inorgánicos convencionalmente usados como materiales para preparaciones farmacéuticas se utilizan como un portador farmacológicamente aceptable que es agregado como excipiente, lubricante, aglomerante, desintegrador para preparaciones sólidas; y solvente, auxiliar de disolución, agente de suspensión, agente de isotonización, agente de amortiguación, agente suavizante y lo similar para preparaciones líquidas. Cuando sea necesario, puede usarse un aditivo para preparaciones farmacéuticas tal como conservante, antioxidante, agente colorante, agente endulcorante y lo similar.

Los ejemplos preferibles del vehículo incluyen lactosa, sacarosa, D-manitol, D-sorbitol, almidón, almidón pregelatinizado, dextrina, celulosa cristalina, hidroxipropil celulosa sustituida inferior, carboximetilcelulosa de sodio, acacia pulverizada, dextrina, pullulan, anhídrido silícico ligero, silicato de aluminio sintético, metasilicato de aluminato de magnesio y lo similar.

Los ejemplos preferibles del lubricante incluyen estearato de magnesio, estearato de calcio, talco, silice coloidal y lo similar.

Los ejemplos preferibles del aglomerante incluyen almidón pregelatinizado, sacarosa, gelatina, acacia pulverizada, metilcelulosa, carboximetilcelulosa, carboximetilcelulosa de sodio, celulosa cristalina, sacarosa,

D-manitol, trehalosa, dextrina, pullulan, hidroxipropil celulosa, hidroxipropil metilcelulosa, polivinilpirrolidona y lo similar.

Los ejemplos preferibles de desintegrador incluyen lactosa, sacarosa, almidón, carboximetilcelulosa, carboximetilcelulosa de calcio, croscaramelosa de sodio, carboximetil almidón sodio, anhídrido silícico sintético, hidroxipropil celulosa sustituida inferior y lo similar.

Los ejemplos preferibles del solvente incluyen agua para la inyección, solución salina fisiológica, solución de Ringer, alcohol, propilenglicol, polietilén glicol, aceite de sésamo, aceite de maíz, aceite de oliva, aceite de semilla de algodón y lo similar.

Los ejemplos preferibles de los auxiliares de disolución incluyen polietilén glicol, propilenglicol, D-manitol, trehalosa, benzoato de bencilo, etanol, trisaminometano, colesterol, trietanolamina, carbonato de sodio, citrato de sodio, salicilato de sodio, acetato de sodio y lo similar.

Los ejemplos preferibles del agente de suspensión incluyen agentes tensioactivos tales como estearíltrietanolamina, sulfato de lauril sodio, lauril aminopropionato, lecitina, cloruro de benzalconio, cloruro de benzetonio, monostearato de glicerol y lo similar; los polímeros hidrófilos tales como el alcohol de polivinilo, polivinilpirrolidona, carboximetilcelulosa de sodio,

metilcelulosa, hidroximetilcelulosa, hidroxietilcelulosa, hidroxipropil celulosa y lo similar; polisorbatos, aceite de castor hidrogenado de polioxietileno; y lo similar.

Los ejemplos preferibles del agente de isotonización incluyen cloruro de sodio, glicerol, D-manitol, D-sorbitol, glucosa y lo similar.

Los ejemplos preferibles del amortiguador incluyen amortiguador de fosfato, amortiguador de acetato, amortiguador de carbonato, amortiguador de citrato y lo similar.

Los ejemplos preferibles del agente suevizante incluyen alcohol bencílico y lo similar.

Los ejemplos preferibles del conservante incluyen p-oxibenzoatos, clorobutanol, bencil alcohol, fenetil alcohol, ácido sórbico, ácido deshidroacético y lo similar.

Los ejemplos preferibles del antioxidante incluyen sulfito, ascorbato y lo similar.

Los ejemplos preferibles del agente colorante incluyen los pigmentos de alquitrán comestible solubles em agua (por ejemplo, colorantes de alimento tales como Color Rojo para Alimento Nos. 2 y 3, Color Amarillo de Alimento Nos. 4 y 5, Color Azul de Alimento Nos. 1 y 2 y lo similar), pigmentos de laca insolubles en agua (por ejemplo, sal de aluminio de pigmento de alquitrán comestible soluble en agua mencionado precedentemente y lo similar), pigmentos naturales (por

ejemplo, beta caroteno, clorofila, rojo de óxido de hierro etc.) y lo similar.

Los ejemplos preferibles del agente edulcorante incluyen sacarina de sodio, glicirrhizinato de dipotasio, aspartamo, stevia y lo similar.

La forma de dosis de la composición farmacéutica mencionado precedentemente es, por ejemplo, un agente oral tal como las tabletas (inclusive tabletas sublinguales y tabletas oralmente desintegrables), cápsulas (inclusive cápsulas blandas y microcápsulas), gránulos, polvos, patillas, jarabes, emulsiones, suspensiones y lo similar; o un agente parenteral tal como inyecciones (por ejemplo, inyecciones hipodérmicas, inyecciones intravenosas, inyecciones intramusculares, inyecciones intraperitoneales, infusiones de goteo etc.), agentes externos (por ejemplo, preparaciones transdérmicas, ungüentos etc.), supositorios (por ejemplo, supositorios rectales, supositorios vaginales etc.), nódulos, preparaciones nasales, preparaciones pulmonares (inhalaciones), preparaciones oftálmicas y lo similar. Éstas pueden administrarse de manera segura mediante una vía oral o vía parenteral.

Estos agentes pueden ser preparaciones de liberación controlada tal como las preparaciones de liberación rápida y preparaciones del liberación prolongada (por ejemplo, microcápsulas de liberación prolongada).

La composición farmacéutica puede ser producida según un método usado convencionalmente en el campo de la preparación farmacéutica, tal como el método descripto en la Farmacopea de Japón y lo similar. Se describen métodos de producción específicos de preparación farmacéutica en detalle a continuación.

Mientras el contenido del compuesto de la presente invención en la composición farmacéutica varía dependiendo de la forma de dosis, la dosis del compuesto de la presente invención y lo similar, es, por ejemplo, de aproximadamente 0,1-100 % en peso.

Por ejemplo, un agente oral es producido agregando, al ingrediente activo, excipientes (por ejemplo, lactosa, sacarosa, almidón, D-manitol y lo similar), desintegradores (por ejemplo, carboximetilcelulosa de calcio y lo similar), aglomerantes (por ejemplo, almidón pregelatinizado, acacia pulverizada, carboximetilcelulosa, hidroxipropil celulosa, polivinilpirrolidona y lo similar), lubricantes (por ejemplo, talco, estearato de magnesio, polietilen glicol 6000 y lo similar) y lo similar, moldeando por compresión la mezcla obtenida, y cuando sea necesario, recubriendo la misma usando una base de recubirmiento para enmascarar el sabor, con propiedad entérica o de liberación prolongada según un método conocido por sí mismo.

Los ejemplos de la base de recubirmiento incluyen una

base de recubrimiento de azúcar, una base de recubrimiento de película soluble en agua, una base de recubrimiento de película entérica, una base de recubrimiento de película de liberación prolongada y lo similar.

Como la base de recubrimiento de azúcar, puede usarse sacarosa, si es necesario, junto con una o más especies seleccionadas de talco, carbonato de calcio precipitado, gelatina, acacia pulverizada, pullulan, cera Carnauba y lo similar.

Como la base de recubrimiento de película soluble en agua, por ejemplo, son utilizados polímeros de celulosa tal como hidroxipropil celulosa, hidroxipropil metilcelulosa, hidroxietilcelulosa, metilhidroxietilcelulosa y lo similar; los polímeros sintéticos tal como dietilaminoacetato de polivinil acetal, copolímero metacrilato de aminoalquilo E [Eudragit E, denominación comercial, Roehm Pharma], polivinilpirrolidona y lo similar; polisacáridos tales como pullulan y lo similar; y lo similar.

Como la base de recubrimiento de película entérica, por ejemplo, se utilizan los polímeros de celulosa tales como ftalato de hidroxipropil metilcelulosa, acetato succinato de hidroxipropil metilcelulosa, carboximetiletilcelulosa, ftalato de acetado de celulosa y lo similar; los polímeros de ácido acrílico tales como copolímero de ácido metacrílico L [Eudragit L, marca de fábrica, Roehm Pharma], copolímero de

ácido metacrílico LD [Eudragit L-30D55, denominación comercial, Roehm Pharma], copolímero de ácido metacrílico S [Eudragit S, denominación comercial, Roehm Pharma] y lo similar; los productos naturales tales como la laca y lo similar; y lo similar.

Como la base de recubrimiento de película de liberación prolongada, por ejemplo, se utilizan los polímeros de celulosa tales como etilcelulosa y lo similar; los polímeros de ácido acrílico tales como copolímero de aminoalquil metacrilato RS [Eudragit RS, denominación comercial, Roehm Pharma], copolímero acrilato de etilo - metacrilato de metilo en suspensión [Eudragit NE, denominación comercial, Roehm Pharma] y lo similar, y lo similar.

Pueden mezclarse dos o más tipos de bases de recubrimiento indicadas precedentemente en una proporción apropiada para el uso. Adicionalmente, un agente de protección ligero tal como el óxido de titanio, óxido férrico y lo similar puede se usado durante el recubrimiento.

Una inyección es producida disolviendo, suspendiendo o emulsionando un ingrediente activo en un solvente acuoso (por ejemplo, agua destilada, solución salina fisiológica, solución Ringer y lo similar) o un solvente aceitoso (por ejemplo, aceite vegetal tal como aceite de oliva, aceite de sésamo, aceite de semilla de algodón, aceite de maíz y lo similar, propilenglicol y lo similar) y lo similar, junto con

un agente de dispersión (por ejemplo, polisorbato 80, aceite de castor polioxietilén hidrogenado 60, polietilén glicol, carboximetilcelulosa, alginato de sodio y lo similar), conservante (por ejemplo, metilparabeno, propilparabeno, alcohol bencílico, clorobutanol, fenol y lo similar), agente de isotonización (por ejemplo, cloruro de sodio, glicerol, D-manitol, D-sorbitol, glucosa y lo similar) y lo similar. En esta etapa, puede usarse en base a la demanda aditivos tales como auxiliares de disolución (por ejemplo, salicilato de sodio, acetato de sodio y lo similar), estabilizadores (por ejemplo, albúmina de suero humana y lo similar), agentes suavizantes (por ejemplo, alcohol bencílico y lo similar) y lo similar.

El compuesto de la presente invencións presenta baja toxicidad (por ejemplo, toxicidad aguda, toxicidad crónica, toxicidad genética, toxicidad reproductiva, toxicidad vascular, carcinogénica), causa mínimos efectos colaterales y puede usarse como un agente para profilaxis o tratamiento o diagnóstico de diversas enfermedades para mamíferos (por ejemplo, ser humano, ganado vacuno, caballo, perro, gato, simio, ratón, rata, especialmente ser humano).

El compuesto de la presente invención posee una actividad inhibitoria de peptidasa superior y puede suprimir la degradación causada por peptidasa de un producto fisiológicamente activo tal como hormonas de péptido,

citoquinas, neurotransmisores y lo similar.

Los ejemplos de las hormonas de péptido incluyen glucagón-similar a péptido-1 (GLP-1), glucagón-similar al péptido-2 (GLP-2), GIP, hormona de liberación de hormona somatotrópica (GHRH) y lo similar.

Los ejemplos de citocinas incluyen la quimioqina talcomo RANTES y lo similar.

Los ejemplos neurotransmisores incluyen neuropéptido Y y lo similar.

Los ejemplos de peptidasas incluyen EC 3.4.11.1 (Leucil aminopeptidasa), EC 3.4.11.2 (alanina aminopeptidasa de nembrana), EC 3.4.11.3 (Cistinil aminopeptidasa), EC 3.4.11.4 (Tripéptido aminopeptidasa), EC 3.4.11.5 (Prolil aminopeptidasa), EC 3.4.11.6 (Aminopeptidasa B), EC 3.4.11.7 (Glutamil aminopeptidasa), EC 3.4.11.9 (Xaa-pro aminopeptidasa), EC 3.4.11.10 (leucil aminopeptidasa Bacteriana), EC 3.4.11.13 (Clostridial aminopeptidasa), EC 3.4.11.14 (Citosol alanil aminopeptidasa), EC 3.4.11.15 (Lisil aminopeptidasa), EC 3.4.11.16 (Xaa-Trp aminopeptidasa), EC 3.4.11.17 (Triptofanil aminopeptidasa), EC 3.4.11.18 (Metionil aminopeptidasa), EC 3.4.11.19 (D-aminopeptidasa estereoespecífica), EC 3.4.11.20 (Aminopeptidasa Ey), EC 3.4.11.21 (Aspartil aminopeptidasa), EC 3.4.11.22 (Aminopeptidasa I), EC 3.4.13.3 (Xaa-His dipeptidasa), EC 3.4.13.4 (Xaa-Arg dipeptidasa), EC 3.4.13.5

(Xaa-metil-His dipeptidasa), EC 3.4.13.7 (Glu-Glu dipeptidasa), EC 3.4.13.9 (Xaa-pro dipeptidasa), EC 3.4.13.12 (Met-Xaa dipeptidasa), EC 3.4.13.17 (dipeptidasa No estereospecifica), EC 3.4.13.18 (Cytosol dipeptidasa no especifica), EC 3.4.13.19 (dipeptidasa de membrana), EC 3.4.13.20 (Beta-Ala-His dipeptidasa), EC 3.4.14.1 (Dipeptidil-peptidasa I), EC 3.4.14.2 (Dipeptidil-peptidasa II), EC 3.4.14.4 (Dipeptidil-peptidasa III), CEE 3.4.14.5 (Dipeptidil-peptidasa IV), EC 3.4.14.6 (Dipeptidil-dipeptidasa), EC 3.4.14.9 (Tripeptidil-peptidasa I), EC 3.4.14.10 (Tripeptidil-peptidasa II), EC 3.4.14.11 (Xaa-Pro dipeptidil-peptidasa) y lo similar según lo clasificado por "International Union of Biochemistry and Molecular Biology". Como peptidasa, puede mencionarse también FAPα, DPP8, DPP9 y lo similar.

De los mismos, son preferibles EC 3.4.14.1, EC 3.4.14.2, EC 3.4.14.4, EC 3.4.14.5, EC 3.4.14.6, EC 3.4.14.9, EC 3.4.14.10 y EC 3.4.14.11. Sobre todo es preferible EC 3.4.14.5 (Dipeptidil-peptidasa IV).

El compuesto de la presente invención puede tener concurrentemente una acción antagónica de glucagón o una acción inhibitoria de CETP además de una acción inhibitoria de peptidasa. Cuando el compuesto de la presente invención posee estas acciones concurrentemente, el compuesto de la presente invención es más eficaz como agente para profilaxis

o tratamiento de diabetes (por ejemplo, diabetes tipo 1, diabetes tipo 2, diabetes mellitus gestational etc.) e hiperlipidemia (por ejemplo, hipertrigliceridemia, hipercolesteremia, hipoHDLemia, hiperlipidemia postprandial etc.).

El compuesto de la presente invención es útil como agente para profilaxis o tratamiento de diabetes (por ejemplo, diabetes tipo 1, diabetes tipo 2, diabetes gestational y lo similar); agente para profilaxis o tratamiento de hiperlipidemia (por ejemplo, hipertrigliceridemia, hipercolesterolemia, hipoHDLemia, hiperlipidemia postprandial y lo similar); agente para profilaxis o tratamiento de arteriosclerosis; agente para profilaxis o tratamiento de tolerancia a glucosa disminuida [IGT]; un secretágogo de insulina; y agente para prevenir el progreso de tolerancia a glucosa disminuida en la diabetes.

Para criterio de diagnóstico de diabetes, "Japan Diabetes Society" informó un nuevo criterio diagnóstico en 1999.

Según este informe, la diabetes es una condición que exhibe en cualquier nivel de glucosa en sangre en ayuno (concentración de glucosa en plasma intravenoso) no inferior de 126 mg/dl, una prueba de tolerancia a glucosa oral de 75 g (75 g OGTT) con nivel de 2h (concentración de glucosa en plasma intravenoso) no inferior de 200 mg/dl, y nivel de

glucosa en sangre sin ayuno (concentración de glucosa en plasma intravenoso) no inferior a 200 mg/dl. Una condición que no se clasifica bajo la diabetes indicada precedentemente y diferente de "una condición que presenta un nivel de glucosa en sangre de ayuno (concentración de glucosa en plasma intravenoso) inferior de 110 mg/dl o una prueba de tolerancia a glucosa oral de 75 g (75 g OGTT) de nivel de 2 h (concentración de glucosa en plasma intravenoso) no inferior de 140 mg/dl" (tipo normal) se denomina un "tipo fronterizo".

Adicionalmente, ADA (Asociación americana de Diabetes) informó un nuevo criterio de diagnóstico de diabetes en 1997 y WHO en 1998.

Según estos informes, la diabetes es una condición que exhibe el nivel de glucosa en sangre en ayuno (concentración de glucosa en plasma intravenoso) no inferior de 126 mg/dl y una prueba de tolerancia a glucosa oral de 75 g de nivel 2 h (concentración de glucosa en plasma intravenoso) no inferior de 200 mg/dl.

Según los informes indicados precedentemente, la tolerancia a glucosa disminuída es una condición que exhibe un nivel de glucosa en sangre en ayuno (concentración de glucosa de plasma intravenoso) no inferior de 126 mg/dl y una prueba de tolerancia a glucosa oral de 75 g de nivel de 2 h (concentración de glucosa en plasma intravenoso) no inferior de 140 mg/dl e inferior de 200 mg/dl. Según el informe de

ADA, una condición que exhibe el nivel de glucosa de sangre en ayuno (concentración de glucosa de plasma intravenoso) no inferior de 110 mg/dl e inferior de 126 mg/dl se denomina IFG (Glucosa en Ayuno Disminuída). Según el informe de WHO, entre el IFG (Glucosa en Ayuno Disminuída), una condición que exhibe una prueba de tolerancia a glucosa oral de 75g de nivel de 2 h (concentración de glucosa en plasma intravenoso) no inferior de 140 mg/dl se denomina IFG (Glusemia en Ayuno Disminuída).

El compuesto de la presente invención también puede usarse como agente para profilaxis o tratamiento de diabetes, tipo fronterizo, tolerancia a glucosa disminuída, IFG (Glucosa en Ayuno Disminuída) e IFG (Glusemia en Ayuno Disminuída), según lo determinado de acuerdo al nuevo criterio de diagnóstico indicado precedentemente. Además, el compuesto de la presente invención puede prevenir el avance del tipo fronterizo, tolerancia a glucosa disminuída, IFG (Glucosa en Ayuno Disminuída) o IFG (Glusemia en Ayuno Disminuída) en la diabetes.

El compuesto de la presente invención también puede ser utilizado como agente para profilaxis o tratamiento de, por ejemplo, complicaciones diabéticas [por ejemplo, neuropatía, nefropatía, retinopatía, catarata, macroangiopatía, osteopenia, coma diabético hiperosmolar, enfermedad infecciosa (por ejemplo, infección respiratoria, infección de

tracto urinario, infección gastrointestinal, infecciones de tejido blando dérmico, infección de miembro inferior y lo similar), gangrena diabética, xerostomia, hipoacusia, desorden cerebrovascular, desorden de circulación de sangre periférica y lo similar], obesidad, osteoporosis, caquexia (por ejemplo, caquexia cancerosa, caquexia tuberculosa, caquexia diabética, caquexia de enfermedad de sangre, caquexia de enfermedad endocrina, caquexia de enfermedad infecciosa o caquexia debido al síndrome de inmunodeficiencia adquirida), hígado graso, hipertensión, síndrome de ovario poliquítico, enfermedad de riñón (por ejemplo, nefropatía diabética, nefritis glomerular, glomeruloesclerosis, síndrome nefrótico, nefroesclerosis hipertensiva, fase final de enfermedad del riñón y lo similar), distrofia muscular progresiva, infarto de miocardio, angina de pecho, accidente cerebrovascular (por ejemplo, infarto cerebral, apoplejía cerebral), enfermedad de Alzheimer, síndrome de Parkinson, ansiedad, demencia, síndrome de resistencia a insulina, Síndrome X, síndrome metabólico, hiperinsulinemia, desorden sensorio inducido por hiperinsulinemia, tumor (por ejemplo, leucemia, cáncer de pecho, cáncer prostático, cáncer de piel y lo similar), síndrome de intestino irritable, diarrea aguda o crónica, enfermedades inflamatorias (por ejemplo, artritis reumatoidea crónica, espondilitis deformante, osteoartritis, lumbago, gota, inflamación postoperatoria o traumática,

tumencia, neuralgia, faringolaringitis, cistitis, hepatitis (inclusive esteatohepatitis no alcohólica), pulmonía, pancreatitis, enteritis, enfermedad inflamatoria de intestino (incluyendo enfermedad inflamatoria de intestino grueso), colitis ulcerativa, lesión de mucosa gástrica (inclusive lesión de mucosal gástrica causada por aspirina) y lo similar), trauma de membrana de mucosa de intestino delgado, absorción gastrointestinal imperfecta, desorden de funcionamiento de testículos, síndrome de obesidad visceral y lo similar.

El compuesto de la presente invención también puede usarse para disminuir la grasa visceral, para suprimir acumulación de grasa visceral, para mejorar el glicometabolismo, para mejorar el metabolismo de lípidos, para suprimir la producción de LDL oxidado, para mejorar el metabolismo de lipoproteina, para mejorar el metabolismo de arteria coronaria, para profilaxis y tratamiento de complicaciones cardiovasculares, para profilaxis y tratamiento de complicaciones de deficiencia cardíaca, para disminución de sangre remanente, para profilaxis y tratamiento de anovulación, para profilaxis y tratamiento de hipertricosis, para profilaxis y tratamiento de hiperandrogenemia, para mejora de función pancreática (célula β), regeneración pancreática (célula β), promoción de regeneración pancreática (célula β), control del apetito y lo

similar.

El compuesto de la presente invención también puede ser utilizado para profiláctica secundaria y prevención de progresión de las diversas enfermedades indicadas precedentemente (por ejemplo, evento cardiovascular tal como el infarto de miocardio y lo similar).

El compuesto de la presente invención es un secretágogo de insulina dependiente de glucosa que promueve selectivamente la secreción de insulina en los pacientes hiperglusémicos (por ejemplo, pacientes que presentan un nivel de glucosa en sangre en ayuno no inferior de 126 mg/dl o prueba de tolerancia a glucosa oral de 75 g (75 g OGTT) a nivel de 2 h no inferior de 140 mg/dl y lo similar). Por consiguiente, el compuesto de la presente invención es útil como agente seguro para profilaxis o tratamiento de diabetes con un bajo riesgo de complicaciones vasculares, inducción de hipoglucemia y lo similar causado por insulina.

El compuesto de la presente invención también es útil como agente terapéutico para diabetes con deficiencia secundaria de sulfonilurea y permite un efecto de secreción de insulina superior y un efecto hipoglusémico para pacientes diabéticos en los cuales los compuestos sulfonilurea y los secretágogos de insulina de acción rápida no proveen un efecto de secreción de insulina, y por consiguiente, no proveen un efecto hipoglusémico suficiente.

Como los compuestos sulfonilurea en la presente, pueden mencionarse compuestos que poseen un esqueleto de sulfonilurea o un derivado del mismo, tal como tolbutamida, glibenclamida, gliclazida, clorpropamida, tolazamida, acetohexamida, gliclopiramida, glimepirida, glipizida, glibuzol y lo similar.

Como el secretágogo de insulina de acción rápida, puede mencionarse un compuesto que promueva la secreción de insulina desde la célula β pancreática de la misma manera como un compuesto de sulfonilurea, aunque no posea un esqueleto de sulfonilurea, tal como los compuestos de glinida (por ejemplo, repaglinida, senaglinida, nateglida, mitiglinida, un hidrato de sal de calcio de los mismos etc.), y lo similar.

Mientras la dosis del compuesto de la presente invención varía, dependiendo del sujeto de administración, vía de administración, enfermedad objetivo, condición y lo similar, el compuesto de la presente invención como ingrediente activo generalmente se aplica en una sola dosis de aproximadamente 0,01-100 mg/kg de peso del cuerpo, preferentemente 0,05-30 mg/kg de peso del cuerpo, más preferentemente 0,1-10 mg/kg de peso del cuerpo, en el caso de, por ejemplo, administración oral a los pacientes diabéticos adultos. Esta dosis se aplica de manera adecuada 1 a 3 veces por día.

El compuesto de la presente invención puede ser

utilizado en combinación con drogas tales como agente terapéuticos de diabetes, agente terapéuticos de complicaciones diabéticas, agente antihiperlipémico, agente antihipertensivo, agente antiobesidad, diurético, agente quimioterapéutico, agente inmunoterapéutico, agente antitrombótico, agente terapéutico de osteoporosis, agente antidemencia, agente para mejorar trastorno eréctil, agente terapéutico para incontinencia o polaquiuria, agente terapéutico para disuria y lo similar (más adelante en la presente denominado droga de combinación). En este caso, la oportunidad de administración del compuesto de la presente invención y droga de combinación no está limitada. Éstas pueden administrarse simultáneamente a un sujeto de administración o pueden ser administradas de una manera alternada. Además, el compuesto de la presente invención y droga de combinación pueden administrarse como dos tipos de preparaciones cada una conteniendo un ingrediente activo, o pueden administrarse como una sola preparación que contiene ambos ingredientes activos.

La dosis de la droga de combinación puede determinarse según sea apropiado basada clínicamente en la dosis empleada. La proporción del compuesto de la presente invención y droga de combinación puede determinarse apropiadamente del sujeto de administración, la vía de administración, la enfermedad designada, condición, combinación y lo similar. Por ejemplo,

cuando el sujeto de administración es ser humano, la droga de combinación es utilizada en una cantidad de 0,01-100 partes en peso por 1 parte en peso del compuesto de la presente invención.

Como el agente terapéutico para diabetes, puedem mencionarse preparaciones de insulina (por ejemplo, preparaciones de insulina animal extraídas del páncreas de bovinos y cerdos; preparaciones de insulina humanas sintetizadas genéticamente usando Escherichia coli o levadura; insulina de zinc; insulina de zinc de protamina; fragmentos o derivados de insulina (por ejemplo, INS-1 etc.), preparación de insulina oral y lo similar), sensibilizadores de insulina (por ejemplo, pioglitazona o una sal del mismo (preferentemente clorhidrato), rosiglitazona o una sal del mismo (preferentemente maleato), Reglixan (JTT-501), GI-262570, Netoglitazona (MCC-555), YM-440, DRF-2593, BM-13.1258, KRP-297, R-119702, Rivoglitazona (C-011), FK-614, los compuestos descriptos en WO99/58510 (por ejemplo, ácido (E)-4-[4-(5-metil-2-fenil-4-oxazolilmetoxil)benciloximino]-4-fenilbutírico), los compuestos descriptos en WO01/38325, Tesaglitazar (AZ-242), Ragaglitazar (NN-622), Muraglitazar (BMS-298585), ONO-5816, BM-13-1258, LM-4156, MBX-102, LY-519818, MX-6054, LY-510929, Balaglitazona (NN-2344), T-131 o una sal del mismo, THR-0921 etc.), agonista de PPARγ, antagonista de PPARγ, agonista dual PPARγ/α, inhibidores de α-

glucosidasa (por ejemplo, voglibosa, acarbosa, miglitol, emiglitato etc.), biguanidas (por ejemplo, fenformin, metformin, buformin o sales de los mismos (por ejemplo, clorhidrato, fumarato, succinato) etc.), secretagogos de insulina [sulfonilurea (por ejemplo, tolbutamida, glibenclamida, gliclazida, clorpropamida, tolazamida, acetohexamida, gliclopiramida, glimepirida, glipizida, glibuzol etc.), repaglinida, senaglinida, nateglida, mitiglinida o hidrato de sal de calcio de los mismos], agonista de GPR40, agonistas de receptor GLP-1 [por ejemplo, GLP-1, GLP-1MR, NN-2211, CA-2993 (exendin-4), BIM-51077, Aib(8,35)hGLP-1(7,37)NH2, CJC-1131], agonistas de amilin (por ejemplo, pramlintida etc.), inhibidores de fosfatase de fosfotirosina (por ejemplo, vanadato de sodio etc.), inhibidores de peptidasa dipeptidil IV (por ejemplo, NVP-DPP-278, PT-100, P32/98, LAF-237, P93/01, T-021, MK-431, BMS-477118 etc.), agonista de β3 (por ejemplo, CL-316243, SR-58611-UN, UL-TG-307, SB-226552, AJ-9677, BMS-196085, AZ40140 etc.), inhibidores de gluconeogénesis (por ejemplo, inhibidor de fosforilasa de glicógeno, inhibidor de glucosa-6-fosfatasa, antagonista de glucagón etc.), inhibidores de SGLT (cotransportador sodio-glucosa) (por ejemplo, T-1095 etc.), inhibidores de deshidrogenasa 11β-hidroxiesteroide (por ejemplo, BVT-3498 etc.), adiponectina o agonistas de los

mismos, inhibidores de IKK (por ejemplo, AS-2868 etc.), las drogas que mejoran la resistencia de leptina, agonistas de receptor de somatoestatina (compuestos descriptos en WO01/25228, WO03/42204, WO98/44921, WO98/45285, WO99/22735 etc.), activadores de glucoquinasa (por ejemplo, Ro-28-1675) y lo similar.

Los ejemplos del agente terapéutico para las complicaciones diabéticas incluyen los inhibidores de aldosa reductasa (por ejemplo, Tolrestat, Epalrestat, Zenarestat, Zopolrestat, Minalrestat, Fidarestat (SNK-860), CT-112 etc.), factores neurotróficos y las drogas que incrementan los mismos (por ejemplo, NGF, NT-3, BDNF, promotores de producción-secreción neurotrofina descriptos en WO01/14372 (por ejemplo, 4-(4-clorofenil)-2-(2-metil-1-imidazolil)-5-[3-(2-metilfenoxi)propil]oxazol etc.) y lo similar), estimuladores de neuranagénesis (por ejemplo, SI-128 etc.), inhibidores de PKC (por ejemplo, mesilato de ruboxistaurina; LY-333531 etc.), inhibidores de AGE (por ejemplo, ALT946, pimagedina, piratoxantina, bromuro de N-fenaciltiazolio (ALT766), ALT-711, EXO-226, Piridorina, Piridoxamina etc.), depuradores de oxigeno reactivo (por ejemplo, ácido tióctico etc.), vasodilatadores cerebral (por ejemplo, tiaprida, mexiletina etc.), agonistas de receptor de somatoestatina (BIM23190) y los inhibidores (ASK-1) de quinasa-1 que regulan la señal de apoptosis.

Los ejemplos del agente antihiperlipémico incluyen compuestos de estatina que son inhibidores de síntesis de colesterol (por ejemplo, cerivastatina, pravastatina, simvastatina, lovastatina, atorvastatina, fluvastatina, itavastatina, rosuvastatina, pitavastatina y sales de los mismos (por ejemplo, sal de sodio, sal de calcio) etc.), inhibidores sintasa de escualeno (por ejemplo, los compuestos descriptos en WO97/10224, tales como ácido N-[[(3R,5S)-1-(3-acetoxi-2,2-dimetilpropil)-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil]piperidin-4-acético etc.), compuestos de fibrato (por ejemplo, bezafibrato, clofibrato, simfibrato, clinofibrato etc.), inhibidores de ACAT (por ejemplo, Avasimibe, Eflucimibe etc.), resinas intercambiadoras de anión (por ejemplo, colestiramina etc.), probucol, drogas de ácido nicotínico (por ejemplo, nicomol, niceritrol y lo similar), icosapentato de etilo, esterols vegetales (por ejemplo, esterol de soja, γ-oryzanol etc.) y lo similar.

Los ejemplos del agente antihipertensivo incluyen los inhibidores de enzima convertidora de angiotensina (por ejemplo, captopril, enalapril, delapril etc.), antagonistas de angiotensina II (por ejemplo, candesartan cilexetil, 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 etc.), antagonistas de calcio (por ejemplo, manidipina, nifedipina, amlodipina, efonidipina, nicardipina etc.), iniciadores de canale de potasio (por ejemplo, levcromakalim, L-27152, AL 0671, NIP-121 etc.), Clonidina y lo similar.

Los ejemplos del agente antiobesidad incluyen agentes antiobesidad que actúan en el sistema nervioso central (por ejemplo, Dexfenfluramina, fenfluramina, fentermina, Sibutramina, amfepramona, dextroanfetamina, Mazindol, fenilpropanolamina, clobenzorex; antagonistas de receptor MCH (por ejemplo, SB-568849; SNAP-7941; compuestos abarcados en WO01/82925 y WO01/87834 etc.); antagonistas de neuropéptido Y (por ejemplo, CP-422935 etc.); antagonistas de receptor canabinoide (por ejemplo, SR-141716, SR-147778 etc.); antagonista de grelina; inhibidores de deshidrogenasa 11b-hidroxiesteroide (por ejemplo, BVT-3498 etc.) y lo similar), inhibidores de lipasa pancreática (por ejemplo, orlistat, ATL-962 etc.), agonists de β3 (por ejemplo, CL-316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085, AZ40140 etc.), anorexiante peptídico (por ejemplo, leptina, CNTF (Factor Neurotrófico Ciliar) etc.), agonistas de colecistoquinina (por ejemplo, lintitript, FPL-15849 etc.), disuasivo de alimentación (por ejemplo, P-57 etc.) y lo similar.

Los ejemplos del diurético incluyen los derivados de

xantina (por ejemplo, salicilato de sodio y teobromina, salicilato de calcio y teobromina etc.), preparaciones de tiazida (por ejemplo, etiazida, ciclopentiazida, triclorometiazida, hidroclorotiazida, hidroflumetiazida, bencilhidroclorotiazida, penflutizida, politiazida, meticlotiazida etc.), preparaciones de antialdosterona (por ejemplo, espironolactona, triamtereno etc.), inhibidores de de carbonato de deshidratasa (por ejemplo, acetazolamida y lo similar), preparaciones de clorobencensulfonamida (por ejemplo, clortalidona, mefrusida, indapamida etc.), azosemida, isosorbido, ácido etacrínico, piretanida, bumetanida, furosemida y lo similar.

Los ejemplos del agente quimioterapéutico incluyen agentes de alquilación (por ejemplo, ciclofosfamida, ifosfamide etc.), antagonistas metabólicos (por ejemplo, metotrexato, 5-fluorouracilo o su derivado, etc.), antibióticos anticáncer (por ejemplo, mitomicina, adriamicina etc.), agentes anticáncer derivados de planta (por ejemplo, vincristina, vindesina, taxol etc.), cisplatina, carboplatina, etoposido y lo similar. De éstos, son preferibles furtulon y neofurtulon los cuales son derivados de 5-fluorouracilo y lo similar.

Los ejemplos del agente inmunoterapéutico incluyen microorganismos o componentes bacterianos (por ejemplo, derivado dipéptido de muramilo, picibanilo etc.),

polisacáridos que poseen actividad de potenciación de inmunidad (por ejemplo, lentinan, sizofiran, crestina etc.), citocinas obtenidas por técnicas de ingeniería genéticas (por ejemplo, interferón, interleucina (IL) etc.), factores estimulantes de colonia (por ejemplo, factor estimulante de colonia de granulocito, eritropoyetina etc.) y lo similar, otorgando preferencia a interleucinas como IL-1, IL-2, IL-12 y lo similar.

Los ejemplos del agente antitrombótico incluyen heparina (por ejemplo, heparina de sodio, heparina de calcio, dalteparina de sodio etc.), warfarina (por ejemplo, warfarina de potasio etc.), drogas antitrombina (por ejemplo, aragatroban etc.), agentes trombolíticos (por ejemplo, uroquinasa, tisoquinasa, alteplasa, nateplasa, monteplasa, pamiteplasa etc.), inhibidores de agregación de plaquetas (por ejemplo, clorhidrato de ticlopidina, cilostazol, icosapentato de etilo, beraprost sodio, clorhidrato de sarpogrelato etc.) y lo similar.

Los ejemplos del agente terapéutico de osteoporosis incluyen alfacalcidol, calcitriol, elcatonina, tirocalcitonina de salmón, estriol, ipriflavona, pamidronato de disodio, alendronato de hidrato de sodio, incadronato de disodio y lo similar.

Los ejemplos del agente antidemencia incluyen tacrina, donepezil, rivastigmina, galantamina y lo similar.

Los ejemplos de agente para mejorar trastorno eréctil incluyen apomorfina, citrato de sildenafil y lo similar.

Los ejemplos del agente terapéutico para incontinencia o polaquiuria incluyen clorhidrato de flavoxato, clorhidrato de oxibutinina, clorhidrato de propiverina y lo similar.

Los ejemplos del agente terapéutico para disuria incluyen inhibidores de esterasa de acetilcolina (por ejemplo, distigmina) y lo similar pueden mencionarse.

Además, las drogas que poseen una acción mejoradora de caquexia establecida en modelos de animal y situaciones clínicas, tales como los inhibidores de ciclooxigenasa (por ejemplo, Indometacina etc.), derivados de Progesterona (por ejemplo, acetato de Megesterol), glucoesteroide (por ejemplo, dexametasona etc.), agentes de metoclopromida, agentes de tetrahidrocanabinol, agentes que mejoran el metabolismo de las grasas (por ejemplo, ácido eicosapentaenoico etc.), hormonas de crecimiento, IGF-1, o anticuerpos a un factor inducido por caquexia tales como TNF-α, LIF, IL-6, Oncostatina M y lo similar, pueden usarse en combinación con el compuesto de la presente invención.

La droga combinatoria es preferentemente una preparación de insulina, un sensibilizador de insulina, un inhibidor de α-glucosidasa, una biguanida, un secretágogo de insulina (preferentemente sulfonilurea) y lo similar.

Dos o más de las drogas de combinación indicadas precedentemente pueden usarse en combinación en una proporción apropiada. Las combinaciones preferibles en el caso de usar dos o más drogas de combinación son, por ejemplo, las indicadas a continuación.

1) un secretágogo de insulina (preferentemente sulfonilurea) y un inhibidor de α-glucosidasa;

2) un secretágogo de insulina (preferentemente sulfonilurea) y una biguanida;

3) un secretágogo de insulina (preferentemente sulfonilurea), una biguanida y un inhibidor de α-glucosidasa;

4) un sensibilizador de insulina y un inhibidor de α-glucosidasa;

5) un sensibilizador de insulina y una biguanida;

6) un sensibilizador de insulina, una biguanida y un inhibidor de α-glucosidasa.

Cuando el compuesto de la presente invención es utilizado en combinación con una droga combinatoria, la cantidad del mismos puede ser reducida dentro de un rango seguro en consideración a la neutralización de estos agentes. Particularmente, la dosis de un sensibilizador de insulina, un secretágogo de insulina (preferentemente sulfonilurea) y una biguanida puede ser reducida en comparación con la dosis normal. Por consiguiente, puede ser prevenido de manera

segura un efecto adverso, que puede ser producido por estos agentes. Adicionalmente, la dosis del agente terapéutico de complicaciones diabéticas, agente antihiperlipémico y agente antihipertensivo puede ser reducida con lo cual el efecto adverso que podría ser producido por estos agentes puede ser prevenido eficazmente.

A continuación se explican los métodos de producción del compuesto de la presente invención.

El compuesto de la presente invención puede ser producido según un método conocido por sí mismo, tal como un método a ser descripto en detalle en lo siguiente, o un método análogo al mismo.

El compuesto (I-a) el cual es un compuesto de la fórmula (I) en donde L es La-CH_2-, (en donde La es un enlace o un grupo de hidrocarburo de cadena bivalente), X es Xa (en donde Xa es un átomo de hidrógeno, un grupo nitro, un grupo acilo, un grupo hidroxilo sustituido, un grupo tiol opcionalmente sustituido, un grupo amino opcionalmente sustituido o un grupo cíclico opcionalmente sustituido), y R^4 es un grupo amino, puede ser producido de acuerdo al Método A siguiente o un método análogo al mismo.

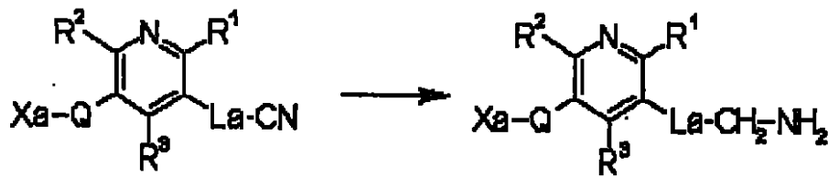
Como el "grupo de hidrocarburo de cadena bivalente" para La, aquellos similares al "grupo de hidrocarburo de cadena bivalente" indicado a manera de ejemplo para el L indicado precedentemente puede mencionarse. La es preferentemente un

enlace o grupo alquileno C_{1-9}.

Adicionalmente, como el "grupo acilo", el "grupo hidroxilo sustituido ", "grupo tiol opcionalmente sustituido", "grupo amino opcionalmente sustituido" y "grupo cíclico opcionalmente sustituido", cada uno para Xa, pueden usarse aquéllos indicados a manera de ejemplo para X mencionados precedentemente.

Cuando Xa es un grupo etoxicarbonilo, entonces Q es preferentemente un grupo de hidrocarburo de cadena bivalente

[Método A]



(II) (I-a)

en donde los símbolos en la fórmula son iguales a los definidos anteriormente.

En este método, el compuesto (II) es sometido a una reacción de reducción para dar el compuesto (I-a).

La reacción de reducción es realizada en presencia de un agente reductor, en un solvente que no influya adversamente en la reacción, de acuerdo a un método convencional.

Como el agente reductor, por ejemplo, pueden mencionarse hidruros de metal tales como el hidruro de bis(2-metoxietoxil)aluminio de sodio, hidruro de diisobutilaluminio y lo similar; los complejos de hidruro de metal tales como el

borohidruro de sodio, cianoborohidruro de sodio, hidruro de aluminio litio, hidruro de aluminio de sodio y lo similar.

La cantidad del agente reductor a ser utilizado generalmente es de 0,1 a 20 equivalente en relación al compuesto (II).

Como el solvente que no influye adversamente en la reacción, por ejemplo, pueden usarse los alcoholes tales como metanol, etanol, propilalcohol, 2-propilalcohol, butanol, isobutanol, terc-butanol y lo similar; los carburos aromáticos tales como benceno, tolueno, xileno y lo similar; los hidrocarburos alifáticos tales como hexano, heptano y lo similar; los éteres tales como dietil éter, diisopropil éter, terc-butilmetil éter, tetrahidrofurano, dioxano, dimetoxietano y lo similar; los ésteres tales como acetato de metilo, acetato de etilo, acetato de n-butilo, acetato de terc-butilo y lo similar; amidas tales como dimetilformamida, dimetilacetamida, N-metilpirrolidona y lo similar. Estos solventes pueden usarse en una mezcla de dos o más tipos de los mismos mezclados en una proporción apropiada.

La temperatura de reacción generalmente es de -70 a 150°C, preferentemente de -20 a 100°C.

El tiempo de reacción generalmente es de 0,1 a 100 hrs, preferentemente de 0,1 a 40 hrs.

La reacción de reducción también puede llevarse a cabo en presencia de un catalizador de metal tal como el paladio-

carbono, negro de paladio, cloruro de paladio, óxido de platino, negro de platino, platino-paladio, níquel Raney, cobalto Raney y lo similar, y una fuente de hidrógeno, en un solvente que no influya adversamente en la reacción.

La cantidad del catalizador de metal a ser usado generalmente es, de 0,001 a 1000 equivalentes, preferentemente 0,01 a 100 equivalente en relación al compuesto (II).

Como la fuente de hidrógeno, por ejemplo, puede mencionarse gas hidrógeno, ácido fórmico, sal de amina de ácido fórmico, sal de ácido fosfínico, hidrazina y lo similar.

Como el solvente que no influye adversamente en la reacción, pueden mencionarse aquéllos usados en la reacción de reducción que utiliza agente reductor mencionados precedentemente.

La temperatura de reacción y el tiempo de reacción son igual que los utilizados para la reacción de reducción que utiliza agente reductor mencionados precedentemente.

Esta reacción puede llevarse a cabo en presencia de amoníaco (por ejemplo, amonio acuoso, amonio-etanol y lo similar) cuando sea necesario. Por reacción en presencia de amonio, puede suprimirse la reacción colateral y puede ser producido el compuesto (I-a) en un elevado rendimiento.

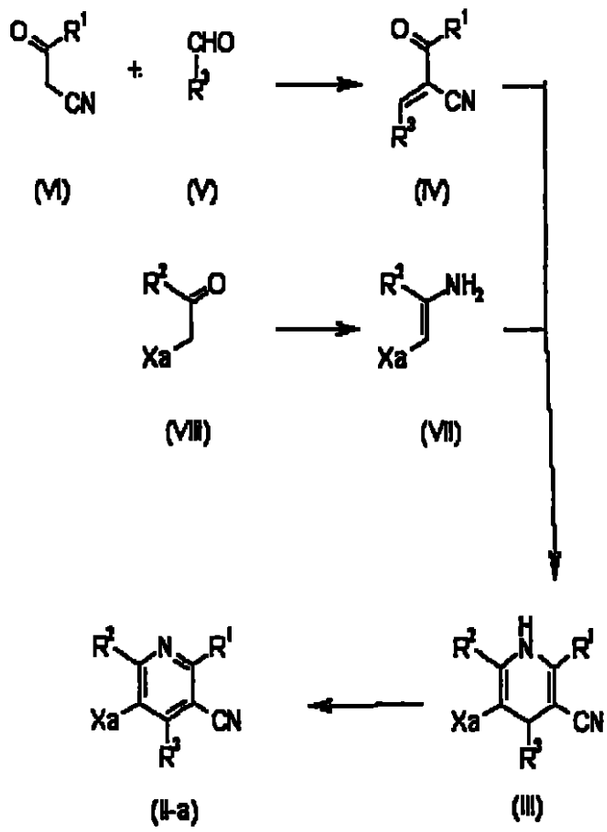
El compuesto (I-a) así obtenido puede ser aislado y

puede ser purificado por un medio de separación y purificación conocido, tal como concentración, concentración bajo presión reducida, extracción por solvente, cristalización, recristalización, transferencia de fase, cromatografía y lo similar.

El compuesto (II) utilizado como el compuesto de comienzo en el Método A indicado precedentemente, puede ser producido según un método conocido por sí mismo.

Por ejemplo, el compuesto (II-a) es un compuesto de la fórmula (II) en donde Q y La son un enlace y Xa es un grupo acilo, puede ser producido según el Método B siguiente.

[Método B]



en donde los símbolos en la fórmula son iguales a los definidos anteriormente.

El compuesto (II-a) puede ser producido según un método conocido por sí mismo; por ejemplo, haciendo reaccionar el compuesto (III) y un oxidante tal como el ácido nítrico diluído, nitrato de cerio diamonio y lo similar, en un solvente que no influya adversamente en la reacción tal como 1,4-dioxano, acetona y lo similar.

El compuesto (III) puede ser producido según un método conocido por sí mismo; por ejemplo, desde el compuesto (IV) y el compuesto (VII) según un método de síntesis de piridina por Hantzch tal como se describe en "Shin Jikken Kagaku Kouza" (Sociedad Química de Japón ed.), Vol. 14, "Synthesis and Reaction of Organic Compound IV", Maruzen (1978), pág. 2057, o un método análogo al mismo.

El compuesto (IV) puede ser producido según un método conocido por sí mismo, por ejemplo, sometiendo el compuesto (VI) y compuesto (V) al método de Knoevenagel conocido.

El compuesto (VII) puede ser producido según un método conocido por sí mismo, por ejemplo, desde el compuesto (VIII) según el método descripto en "Synthesis" (1999), vol. 11, págs. 1951-1960; "Journal of Chemical Society Perkin Transactions 1", (2002), páginas 1663-1671 y lo similar, o un método análogo al mismo.

El compuesto (V), compuesto (VI) y compuesto (VIII)

mencionados precedentemente pueden ser producidos según un método conocido por sí mismo.

El compuesto (I-b) que es un compuesto de la fórmula (I) en donde R^4 es un grupo amino mono- o disustituido por el grupo alquilo C_{1-10}, puede ser producido sometiendo el compuesto (I-c) que es un compuesto de la fórmula (I) en donde R^4 es un grupo amino, a una reacción de alquilación.

Esta reacción se lleva a cabo (1) en presencia de base cuando sea necesario, usando un agente de alquilación en un solvente que no influya adversamente en la reacción, ó (2) en presencia de un agente reductor cuando sea necesario, usando un compuesto carbonilo en un solvente que no influya adversamente en la reacción, según un método conocido.

Como el agente de alquilación en la presente, por ejemplo, puede mencionarse alquilhaluro C_{1-10}, sulfonato de alquilo C_{1-10} y lo similar.

Como el compuesto carbonilo, por ejemplo, pueden mencionarse los aldehídos, cetonas y lo similar.

La cantidad del agente de alquilación y el compuesto carbonilo a ser usada es preferentemente desde aproximadamente 1 hasta aproximadamente 5 equivalentes en relación al compuesto (I-c).

Como la base, por ejemplo, pueden mencionarse sal de metal alcalino tal como hidróxido de sodio, carbonato de potasio y lo similar; amina tal como piridina, trietilamina y

lo similar; hidruros de metal tal como hidruro de sodio y lo similar; alcóxidos de metal alcalino tal como metóxido de sodio, t-butóxido de potasio y lo similar.

La cantidad de la base a ser usada es preferentemente desde aproximadamente 1 hasta aproximadamente 5 equivalentes en relación al compuest (I-c).

Como el agente de reducción, por ejemplo, pueden mencionarse hidruros de metal como el hidruro de diisobutilaluminio y lo similar; los complejos de hidruro de metal tal como cianoborohidruro de sodio y lo similar.

La cantidad de agente de reducción a ser usado generalmente es desde 0,1 hasta 20 equivalentes en relación al compuesto (I-c).

La reacción que usa el compuesto de carbonilo mencionado también puede llevarse a cabo en presencia de un catalizador de metal tal como paladio-carbono y lo similar y una fuente de hidrógeno, sin agente reductor, en un solvente que no influya adversamente en la reacción.

La cantidad del catalizador de metal a ser usado es preferentemente desde 0,01 hasta 100 equivalentes en relación al compuesto (I-c).

Como la fuente de hidrógeno, por ejemplo, puede mencionarse gas hidrógeno, ácido fórmico, sal amina de ácido fórmico y lo similar.

Como el "solvente que no influya adversamente en la

reacción" utilizado para la reacción de alquilación, por ejemplo, pueden mencionarse los hidrocarburos aromáticos tales como tolueno y lo similar; los éteres tales como tetrahidrofurano y lo similar; hidrocarburos halogenados tales como cloroformo y lo similar; amidas tales como N,N-dimetilformamida y lo similar; sulfóxidos tales como dimetilsulfóxido y lo similar. Estos solventes pueden usarse en una mezcla de los mismos en una proporción apropiada.

En la reacción de alquilación, la temperatura de reacción es preferentemente desde aproximadamente -10 hasta aproximadamente 100°C.

En la reacción de alquilación, el tiempo de reacción es generalmente desde aproximadamente 0,5 hasta aproximadamente 20 hrs.

El compuesto (I-b) así obtenido puede ser aislado y puede ser purificado por un medio de separación y purificación conocido, tal como concentración, concentración bajo presión reducida, extracción por solvente, cristalización, recristalización, transferencia de fase, cromatografía y lo similar.

Al producir el compuesto de la presente invención, cuando el compuesto de comienzo posee grupo amino, grupo carboxilo, grupo hidroxilo o grupo carbonilo como sustituyente, puede ser introducido un grupo protector utilizado generalmente en la química del péptido y lo similar

en estos grupos. Al eliminar el grupo protector según sea necesario después de la reacción, puede ser obtenido el compuesto objetivo.

Por ejemplo, el grupo protector amino incluye grupo formilo, grupo alquil C_{1-6}-carbonilo (por ejemplo, acetilo, propionilo y lo similar), grupo alcoxicarbonilo C_{1-6} (por ejemplo, metoxicarbonilo, etoxicarbonilo, terc-butoxicarbonilo y lo similar), grupo benzoilo, grupo aralquil C_{7-13}-carbonilo (por ejemplo, bencilcarbonilo y lo similar), grupo aralquiloxi C_{7-13}-carbonilo (por ejemplo, benciloxicarbonilo, 9-fluorenilmetoxicarbonilo y lo similar), grupo tritilo, grupo ftaloilo, grupo N,N-dimetilaminometileno, grupo sililo (por ejemplo, trimetilsililo, trietilsililo, dimetilfenilsililo, terc-butildimetilsililo, terc-butildietilsililo y lo similar), grupo alquenilo C_{2-6} (por ejemplo, 1-alilo y lo similar) y lo similar. Estos grupos son opcionalmente sustituidos por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo y lo similar), grupo alcoxilo C_{1-6} (por ejemplo, metoxilo, etoxilo, propoxilo y lo similar), grupo nitro y lo similar.

El grupo protector carboxilo es por ejemplo, grupo alquilo C_{1-6} (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, terc-butilo y lo similar), grupo aralquilo C_{7-13} (por ejemplo, bencilo y lo similar), grupo fenilo, grupo tritilo, grupo sililo (por ejemplo, trimetilsililo, trietilsililo,

dimetilfenilsililo, terc-butildimetilsililo, terc-butildietilsililo y lo similar), grupo alquenilo C_{2-6} (por ejemplo, 1-alilo y lo similar) y lo similar. Estos grupos son opcionalmente sustituidos por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo y lo similar), grupo alcoxilo C_{1-6} (por ejemplo, metoxilo, etoxilo, propoxilo y lo similar) o grupo nitro y lo similar.

El grupo protector hidroxilo es por ejemplo, grupo alquilo C_{1-6} (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, terc-butilo y lo similar), grupo fenilo, grupo tritilo, grupo aralquilo C_{7-13} (por ejemplo, bencilo y lo similar), grupo formilo, grupo alquil C_{1-6}-carbonilo (por ejemplo, acetilo, propionilo y lo similar), grupo benzoilo, grupo aralquil C_{7-13}-carbonilo (por ejemplo, bencilcarbonilo y lo similar), grupo 2-tetrahidropiranilo, grupo 2-tetrahidrofuranilo, grupo sililo (por ejemplo, trimetilsililo, trietilsililo, dimetilfenilsililo, terc-butildimetilsililo, terc-butildietilsililo y lo similar), grupo alquenilo C_{2-6} (por ejemplo, 1-alilo y lo similar) y lo similar. Estos grupos son opcionalmente sustituidos por 1 a 3 átomo(s) halógenos (por ejemplo, flúor, cloro, bromo, iodo y lo similar), grupo alquilo C_{1-6} (por ejemplo, metilo, etilo, propilo y lo similar), grupo alcoxilo C_{1-6} (por ejemplo, metoxilo, etoxilo, propoxilo y lo similar) o grupo nitro y lo similar.

El grupo protector carbonilo es por ejemplo, acetal cíclico (por ejemplo, 1,3-dioxano y lo similar), acetal no cíclico (por ejemplo, dialquil C_{1-6} acetal y lo similar) y lo similar.

La introducción y eliminación de estos grupos protectores puede seguir un método conocido por sí mismo, por ejemplo, un método descripto en "Protective Groups in Organic Synthesis", John Wiley & Sons (1980) y lo similar. Por ejemplo, es utilizado un método que emplea ácido, base, luz UV, hidrazina, fenil hidrazina, N-metilditiocarbamato de sodio, fluoruro de tetrabutilamonio, acetato de paladio, haluro de trialquilsililo (por ejemplo, ioduro de trimetilsililo, bromuro de trimetilsililo y lo similar) y lo similar, reducción y lo similar.

Cuando el compuesto de comienzo puede formar una sal al producir el compuesto de la presente invención, puede usarse el compuesto en forma de una sal. Como tal sal, pueden usarse las indicadas anteriormente a manera de ejemplo para la sal del compuesto (I).

Cuando el compuesto (I) contiene un isómero óptico, un estereoisómero, un isómero de posición o un isómero rotatorio, éstos también están abarcados en el compuesto (I), y pueden obtenerse como un solo producto según un método de síntesis y método de separación conocido por sí mismo. Por ejemplo, cuando el compuesto (I) tiene un isómero óptico, un

isómero óptico resuelto de este compuesto también está abarcado en el compuesto (I).

El isómero óptico puede ser producido por un método conocido por sí mismo. Para ser específico, es utilizado un compuesto intermedio sintético ópticamente activo, o el producto de racemato final es sometido a resolución óptica según un método convencional para dar un isómero óptico.

El método de resolución óptica puede ser un método conocido por sí mismo, tal como un método de recristalización fraccionario, un método de columna de quiral, un método de diastereómero y lo similar.

1) Método de recristalización fraccionaria

Una sal es realizada de un racemato con un compuesto ópticamente activo (por ejemplo, (+)-ácido mandélico, (-)-ácido mandélico, (+)-ácido tartárico, (-)-ácido tartárico, (+)-1-fenetilamina, (-)-1-fenetilamina, cinconina, (-)-cinconidina, brucina y lo similar), el cual es separado por un método de recristalización fraccionario y se obtiene un isómero óptico libre por una etapa de neutralización cuando se desee.

2) Método de columna quiral

Un racemato o una sal del mismo es aplicada a una columna para la separación desde un isómero óptico (columna quiral) para permitir la separación. En el caso de una cromatografía líquida, por ejemplo, se aplica una mezcla de

un isómero óptico a una columna quiral como "ENANTIO-OVM" (fabricada por "Tosoh Corporation") o serie "CHIRAL" (fabricada por "Daicel Chemical Industries, Ltd.") y lo similar, y es desarrollada con agua, varios amortiguadores (por ejemplo, amortiguador de fosfato) y solventes orgánicos (por ejemplo, etanol, metanol, isopropanol, acetonitrilo, ácido trifluoracético, dietilamina y lo similar) solamente o en una mezcla para separar el isómero óptico. En el caso de una cromatografía gaseosa, por ejemplo, una columna quiral como "CP-Chirasil-DeX CB" (fabricada por "GL Sciences Inc.") y lo similar es utilizado para permitir la separación.

3) Método de diastereómero

Una mezcla racémica es preparada en una mezcla diastereomérica para reacción química con un reactivo ópticamente activo que es preparado en una sola substancia por un medio de separación típico (por ejemplo, recristalización fraccionaria, método de cromatografía y lo similar) y lo similar, y es sometida a un tratamiento químico tal como hidrólisis y lo similar para separar una fracción del reactivo ópticamente activo, con lo cual se obtiene un isómero óptico. Por ejemplo, cuando el compuesto (I) contiene grupo hidroxilo o grupo amino primarioo o secundario en una molécula, el compuesto y un ácido orgánico ópticamente activo (por ejemplo, MTPA [ácido α-metoxi-α-(trifluorometil)fenilacético], (-)-ácido mentoxiacético y lo

similar) y lo similar es sometido a reacción de condensación para dar un diastereómero en forma de éster o diastereómero en forma de amida, respectivamente. Cuando el compuesto (I) posee un grupo carboxilo, este compuesto y una amina ópticamente activa o un reactivo de alcohol ópticamente activo se somete a reacción de condensación para dar un diastereómero en forma de amida o diastereómero en forma de éster, respectivamente. El diastereómero separado es convertido a un isómero óptico del compuesto original por hidrólisis ácida o reacción de hidrólisis básica.

El compuesto (I) puede estar en la forma de un cristal.

El cristal del compuesto (I) (en adelante en la presente a veces denominado cristal de la presente invención) puede ser producido por cristalización del compuesto (I) por un método de cristalización conocido por sí mismo.

Los ejemplos del método de cristalización incluyen la cristalización de una solución, cristalización desde vapor, cristalización de una forma fundida y lo similar.

La "cristalización de una solución" es típicamente un método que incluye el cambio de un estado no saturado al estado sobresaturado por factores variables involucrados en la solubilidad de compuestos (composición de solvente, pH, temperatura, fuerza iónica, estado de óxido-reducción etc.) o cantidad de solvente. Para ser específico, por ejemplo, el método de concentración, método de recocido, mét do de

reacción (método de difusión, método de electrólisis), método de crecimiento hidrotérmico, método de agente fundente y lo similar pueden mencionarse.

Los ejemplos del solvente a ser utilizado incluyen los hidrocarburos aromáticos (por ejemplo, benceno, tolueno, xileno etc.), hidrocarburos halogenados (por ejemplo, diclorometano, cloroformo etc.), hidrocarburos saturados (por ejemplo, hexano, heptano, ciclohexano etc.), éteres (por ejemplo, dietil éter, diisopropil éter, tetrahidrofurano, dioxano etc.), nitrilos (por ejemplo, acetonitrilo etc.), cetonas (por ejemplo, acetona etc.), sulfóxidos (por ejemplo, dimetilsulfóxido etc.), amidas ácidas (por ejemplo, N,N-dimetilformamida y lo similar), ésteres (por ejemplo, acetato de etilo etc.), alcoholes (por ejemplo, metanol, etanol, isopropil alcohol etc.), agua y lo similar. Estos solventes son utilizados exclusivamente o en combinación de dos o más en una proporción conveniente (por ejemplo, 1:1 a 1:100 (proporción de volumen)).

Por ejemplo, la "cristalización desde vapor" es un método de vaporización (método de tubo sellado, método de corriente de gas), método de reacción en fase gas, método de transporte químico y lo similar.

La "cristalización desde una forma fundida" es, por ejemplo, el método de congelación normal (método de Czockralski, método del gradiente de temperatura, método de

Bridgman), método de fusión local (método de nivelación de zona, método de zona flotante), método de crecimiento especial (método VLS, método epitaxial de fase líquida) y lo similar.

Los ejemplos preferibles del método de cristalización incluyen un método que incluye disolución del compuesto (I) en un solvente conveniente (por ejemplo, alcoholes tales como metanol, etanol etc., y lo similar) a una temperatura desde 20 hasta 120°C y enfriar la solución resultante a una temperatura no superior a la temperatura de disolución (por ejemplo, 0 a 50°C, preferentemente 0 a 20°C) y lo similar.

Los cristales de la presente invención así obtenidos pueden ser aislados mediante, por ejemplo, filtración y lo similar.

En la presente descripción, el punto de fusión se refiere al medido utilizando, por ejemplo, el aparato de la medición de punto de microfusión ("Yanako, MP-500D" o "Büchi, B-545") o dispositivo DSC (examen de calorimetría diferencial) ("SEIKO, EXSTAR6000") y lo similar.

En general, los puntos de fusión varían, dependiendo de los aparatos de medición, las condiciones de medición y lo similar. El cristal en la presente descripción puede demostrar un punto de fusión diferente al descripto en la presente descripción, con la condición que esté dentro del rango de error general.

El cristal de la presente invención es superior en propiedades fisicoquímicas (por ejemplo, punto de fusión, solubilidad, estabilidad etc.) y propiedades biológicas (por ejemplo, farmacocinética (absorción, distribución, metabolismo, excreción), expresión de eficacia etc.), y es sumamente útil como un agente farmacéutico.

La presente invención será explicada en más detalle por los siguientes Ejemplos, Ejemplos Experimentales y Ejemplos de Formulación. Éstos no limitan la presente invención y la presente invención puede ser modificada dentro de un rango que no se aparte del alcance de la invención.

Las abreviaturas en los Ejemplos tienen los significados siguientes:

s: singulete, d: doblete, t: triplete, q,: cuarteto,

m: multiplete, brs: singulete ancho,

J: constante de acoplamiento,

4-Me-fenilo,: 4-metilfenilo,

4-F-fenilo: 4-fluorofenilo,

2,6-di-F-fenilo: 2,6-difluorofenilo.

En los Ejemplos, la temperatura ambiente significa una temperatura desde 1 hasta 30°C, y % significa por ciento en peso, a menos que sea indicado de otra manera.

Ejemplo 1

Metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) Una suspensión de hidruro de sodio (60% en aceite; 8,0 g; 0,2 mol) en tetrahidrofurano (80 mL) fue calentada bajo reflujo agitando vigorosamente.. Una mezcla de isovalerato de metilo (11,6 g; 0,1 mol), acetonirtilo (10,5 mL; 0,2 mol) y tetrahidrofurano (25 mL) fueron agregados por gotas a la suspensión obtenida durante 30 min., y la mezcla fue calentada bajo reflujo por 5 hrs. A la mezcla de reacción se le permitió enfriar a la temperatura ambiente, y fue agregado 2-propilalcohol (5 mL) a la misma. La mezcla fue agitada a la temperatura ambiente por 30 min. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo fue disuelto en agua (100 mL) y fue lavada consecutivamente con hexano y una solución mezcla hexano-dietil éter. La capa acuosa fue acidificada con ácido clorhídrico concentrado y fue extractada con dietil éter. El extracto fue lavado con agua y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida para dar 5-metil-3-oxohexannitrilo (12,6 g, rendimiento 100%) como un aceite amarillo. El aceite amarillo obtenido fue utilizado en la etapa siguiente sin purificación adicional.

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 2,05-2,30 (1H; m); 2,50 (2H; d; J = 7,0 Hz); 3,43 (2H; s).

2) Una mezcla de 5-metil-3-oxohexannitrilo (5,0 g, 40 mmol), p-tolualdehído (4,8 g; 40 mmol), piperidina (0,34 g; 4,0 mmol), ácido acético (0,48 g; 8,0 mmol) y tolueno (200

mL) fue calentada bajo reflujo por 12 hrs. usando una trampa Dean-Stark. A la mezcla de reacción se le permitió enfriar a la temperatura ambiente, fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue disuelto en metanol (50 mL). Metilo 3-aminocrotonato (4,6 g; 40 mmol) fue agregado a los mismos y la mezcla fue calentada bajo reflujo por 6 hrs. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo fue purificado por cromatografía en columna de gel de sílice para dar metil 5-ciano-6-isobutil-2-metil-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (7.45 g, rendimiento 57%) como cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ:0,93 (3H; d; J = 6,6 Hz); 0,98 (3H; d; J = 6,6 Hz); 1,80-2,00 (1H; m); 2,10-2,35 (2H; m); 2,30 (3H; s); 2,36 (3H; s); 3,58 (3H; s); 4,57 (1H; s); 5,68 (1H; brs); 7,00-7,20 (4H; m).

3) Metil 5-ciano-6-isobutil-2-metil-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (7,3 g; 22,5 mmol) fue disuelto en 1,4-dioxano (20 mL), y fue agregado 2N ácido nítrico (100 mL) a los mismos y la mezcla fue agitada a 70°C por 1 hr. Mientras se agita en un baño de hielo, acetato de etilo (100 mL) y fue agregado 2N solución de hidróxido de sodio acuosa (100 mL) a la misma. La capa acuosa fue separada y fue extraída con acetato de etilo. Se combinaron la capa

orgánica y el extracto, y la mezcla fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar metil 5-ciano-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (5.94 g, rendimiento 82%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,6 Hz); 2,20-2,35 (1H; m); 2,41 (3H; s); 2,63 (3H; s); 2,95 (2H; d; J = 7,4 Hz); 3,60 (3H; s); 7,20-7,30 (4H; m).

4) Una mezcla de metil 5-ciano-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,00 g; 3.10 mmol), níquel Raney (4 mL), 25% amonio acuoso (6 mL), tetrahidrofurano (15 mL), metanol (45 mL) fue agitado en un tubo sellado bajo 5,098 kg/cm^2 de atmósfera de hidrógeno a la temperatura ambiente por 6 hrs. La mezcla de reacción fue filtrada y el filtrado fue concentrado bajo presión reducida. El residuo fue dividido entre acetato de etilo y solución 10% de carbonato de potasio acuosa. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,97 g; rendimiento 95%) como cristales amarillos.

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,39 (2H; brs); 2,15-2,30 (1H; m); 2,39 (3H; s); 2,53 (3H; s); 2,80 (2H; d; J = 7,2 Hz); 3,50 (3H; s); 3,66 (2H; s); 7,11 (2H; d; J = 8,0 Hz); 7,21 (2H; d; J = 8,0 Hz).

Punto de fusión: 56-57°C

Ejemplo 2

Dihidrocloruro de ácido 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico

1) A una solución de metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,90 g; 2,76 mmol) en tetrahidrofurano (25 mL) fue agregado dicarbonato de di-terc-butilo (0,76 mL; 3,31 mmol), y la mezcla fue agitada a la temperatura ambiente por 12 hrs. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo fue purificado por cromatografía en columna de gel de sílice para dar metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,16 g; rendimiento 98%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,10-2,30 (1H; m); 2,39 (3H; s); 2,54 (3H; s); 2,78 (2H; d; J = 7,2 Hz); 3,50 (3H; s); 4,15 (2H; d; J = 4,9 Hz); 4,24 (1H; t; J = 4,9 Hz); 7,06 (2H; d; J = 7,9 Hz); 7,20 (2H; d; J = 7,9 Hz).

2) A una solución de metil 5-{[(terc-

butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,0 g; 2,34 mmol) en metanol (30 mL) fue agregado 1N solución de hidróxido de sodio acuosa (10 mL), y la mezcla fue calentada bajo reflujo durante 3 días. A la mezcla de reacción se le permitió enfriar a la temperatura ambiente, fue acidificada con 0,5N ácido clorhídrico y fue extractada con acetato de etilo. El extracto fue lavado con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue cristalizado desde agua-metanol para dar ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (0,58 g; rendimiento 60%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,87 (6H; d; J = 6,4 Hz); 1,39 (9H; s); 1,95-2,10 (1H; m); 2,38 (3H; s); 2,67 (3H; s); 2,75 (2H; d; J = 7,2 Hz); 4,13 (2H; d; J = 4,7 Hz); 4,30 (1H; t; J = 4,7 Hz); 7,15 (2H; d; J = 7,9 Hz); 7,22 (2H; d; J = 7,9 Hz).

3) A una solución de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (0,20 g; 0,48 mmol) en 1,4-dioxano (4 mL) fue agregado 4N solución de cloruro de hidrógeno 1,4-dioxano (4 mL, 16 mmol), y la mezcla fue agitada a la temperatura ambiente por 2 hrs. La mezcla de reacción fue concentrada bajo presión reducida, y el sólido blanco

obtenido fue lavado con diisopropil éter para dar dihidroclouro de ácido 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (0,18 g; rendimiento 95%) como un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,05-2,30 (1H; m); 2,38 (3H; s); 2,65 (3H; s); 3,02 (2H; s); 3,83 (2H; d; J = 5,5 Hz); 7,26 (2H; d; J = 8,2 Hz); 7,32 (2H; d; J = 8,2 Hz); 8,45 (3H; brs).

Ejemplo 3

Dihidrocloruro de 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinamida

1) Una mezcla de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (0,11 g; 0,27 mmol), sal de amonio 1-hidroxi-1H-benzotriazol (0,10 g; 0,65 mmol), hidrocloruro de 1-etil-3-(3-dimetilaminopropil)carbodiimida (0,13 g; 0,65 mmol) y N,N-dimetilformamida (10 mL) fue agitado a temperatura ambiente durante 2.5 días. La mezcla de reacción fue dividida entre acetato de etilo (100 mL) y 0,1 M solución de ácido cítrico acuosa (50 mL). Se combinaron la capa orgánica y un extractó obtenidos extrayendo la capa acuosa con acetato de etilo, y la mezcla fue lavada consecutivamente con carbonato hidrógeno de sodio acuoso saturado y solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y

el residuo fue purificado por cromatografía en columna de gel de sílice para dar terc-butil {[5-(aminocarbonil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0.090 g, rendimiento 82%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,10-2,30 (1H; m); 2,39 (3H; s); 2,61 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 4,14 (2H; d; J = 4,7 Hz); 4,15-4,30 (1H; m); 5,22 (1H; brs); 5,41 (1H; brs); 7,11 (2H; d; J = 7,9 Hz); 7,23 (2H, d, J = 7,9 Hz).

2) Dihidrocloruro de 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinamida (0,050 g, rendimiento 82%) fue obtenido como polvo blanco de terc-butil {[5-(aminocarbonil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,065 g; 0,16 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,05-2,30 (1H; m); 2,37 (3H; s); 2,66 (3H; s); 3,02 (2H; s); 3,82 (2H; d; J = 4,9 Hz); 7,20-7,35 (4H; m); 7,54 (1H; brs); 7,84 (1H; brs); 8,32 (3H; brs).

Ejemplo 4

Dihidrocloruro de 5-(aminometil)-N-(3-amino-3-oxopropil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinamida

1) Una mezcla de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-

metilfenil)nicotínico (0,12 g; 0,29 mmol), hidrocloruro de β-alaninamida (0.055 g, 0.44 mmol), 1-hidroxi-1H-benzotriazol (0,059 g; 0,44 mmol), hidrocloruro de 1-etil-3-(3-dimetilaminopropil)carbodiimida (0,084 g; 0,44 mmol), trietilamina (0,061 mL; 0,44 mmol) y N,N-dimetilformamida (5 mL) fue agitado a temperatura ambiente por 14 hrs. La mezcla de reacción fue dividida entre acetato de etilo-tetrahidrofurano (1:1, 100 mL) y 0,1 M solución ácido cítrico acuosa (100 mL). Se combinaron la capa orgánica y un extracto obtenidos extrayendo la capa acuosa con acetato de etilo, y la mezcla fue lavada consecutivamente con carbonato hidrógeno de sodio acuoso saturado y solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar terc-butil {[5-[(3-amino-3-oxopropil)amino]carbonil-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,075 g; rendimiento 54%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,38 (9H; s); 1,98 (2H; t; J = 6,0 Hz); 2,10-2,25 (1H; m); 2,38 (3H; s); 2,55 (3H; s); 2,76 (2H; d; J = 7,2 Hz); 3,36 (2H; q; J = 6,0 Hz); 4,11 (2H; d; J = 5,5 Hz); 4,23 (1H; brs); 5,23 (1H; brs), 5,38 (1H; brs); 6,22 (1H; t; J = 5,5 Hz); 7,09 (2H; d; J = 8,1 Hz); 7,19 (2H; d; J = 8,1 Hz).

2) Dihidrocloruro de 5-(aminometil)-N-(3-amino-3-oxopropil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinamida (0,048 g, 99%) fue obtenido como polvo blanco de terc-butil {[5-[(3-amino-3-oxopropil)amino]carbonil-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,050 g; 0,10 mmol) según un método similar al método del Ejemplo 2-3). ^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 1,98 (2H; t; J = 6,7 Hz); 2,10-2,25 (1H; m); 2,37 (3H; s); 2,57 (3H; s); 2,96 (2H; brs); 3,09 (2H; q; J = 6,7 Hz); 3,82 (2H; d; J = 5,3 Hz); 6,82 (1H; brs); 7,21 (2H; d; J = 8,0 Hz); 7,27 (2H; d; J = 8,0 Hz); 7,28 (1H; brs); 8,24 (3H; brs); 8,36 (1H; brs).

Ejemplo 5

[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetonitrilo

1) Una suspensión de metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (3,4 g; 7,9 mmol) en tolueno (80 mL) fue enfriada a -78°C, y 0,95 M solución de hidruro de diisobutilaluminio tolueno (33 mL, 32 mmol) fue agregada a la misma por gotas durante 15 min. Después de agitar a -78°C por 1,5 hrs., se permite calentar la mezcla a 0°C, y adicionalmente fue agitada por 30 min. El metanol (1 mL) y el hidrato de sulfato de sodio 10 (10,2 g, 32 mmol) fue agregado consecutivamente a la mezcla de reacción, y la mezcla fue agitada a temperatura ambiente por 1 hr. El

material insoluble fue filtrado, y el filtrado fue concentrado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice para dar terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,9 g, rendimiento 60%) como un aceite.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,32 (9H; s); 2,13-2,25 (1H; m); 2,42 (3H; s); 2,68 (3H; s); 2,75 (2H; d; J = 7,4 Hz); 4,05 (2H; d; J = 4,7 Hz); 4,19 (1H; brs); 4,36 (2H; d; J = 5,7 Hz); 7,05 (2H; d; J = 7,9 Hz); 7,24-7,26 (2H; m).

2) Una mezcla de terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,50 g, 1,3 mmol), trietilamina (0,35 mL; 2,5 mmol) y tetrahidrofurano (10 mL) fue enfriada a 0°C, y fue agregado a la misma cloruro de metansulfonilo (0.22 g, 1.9 mmol) por gotas. Después de agitar a temperatura ambiente por 30 min, la mezcla de reacción fue vertida en carbonato de hidrógeno de sodio acuoso saturado, y la mezcla se extrajo con acetato de etilo. El extracto fue secado sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo fue disuelto en dimetilsulfóxido (5 mL), y cianuro de potasio (0,41 g; 6,3 mmol) fue agregado a la misma. La mezcla fue agitada a 60°C por 30 min. Fue agregado acetato de etilo a la mezcla de reacción, y la mezcla fue lavada consecutivamente con agua y solución salina saturada y fue

secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar terc-butil {[5-(cianometil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,36 g; rendimiento 72%) como un aceite.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,38 (9H; s); 2,16-2,25 (1H; m); 2,43 (3H; s); 2,66 (3H; s); 2,77 (2H; d; J = 7,2 Hz); 3,31 (2H; s); 4,07 (2H; d; J = 4,7 Hz); 7,04 (2H; d; J = 8,0 Hz); 7,31 (2H; d; J = 8,0 Hz).

3) Fue agregado ácido trifluoracético (5 mL) al terc-butil {[5-(cianometil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,11 g, 0,27 mmol), y la mezcla fue agitada a la temperatura ambiente por 15 min. La mezcla de reacción fue vertida en carbonato hidrógeno de sodio acuoso saturado, y la mezcla se extrajo con acetato de etilo-tetrahidrofurano. El extracto fue secado sobre sulfato de magnesio anhidro, y el solvente fue evaporado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice para dar [5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetonitrilo (0,084 g, rendimiento 99%) como un aceite.

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 2,11-2,22 (1H; m); 2,45 (3H; s); 2,66 (3H; s); 2,80 (2H; d; J = 7,2 Hz); 3,47

(2H; s); 3,74 (2H; brs); 7,17 (2H; d; J = 7,8 Hz); 7,42 (2H; d; J = 7,8 Hz).

Ejemplo 6

Dihidrocloruro de 2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetamida

1) A una solución de terc-butil {[5-(cianometil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,90 g; 2,2 mmol) en etanol (20 mL) fue agregado 2N solución de hidróxido de sodio acuosa (5,5 mL; 11 mmol), y la mezcla fue calentada bajo reflujo por 2 hrs. Fue agregado 6N ácido clorhídrico para acidificar la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto fue lavado con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida para dar terc-butil {[5-(2-amino-2-oxoetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,25 g; rendimiento 27%) como un sólido incoloro.

2) Fue agregado ácido trifluoracético (5 mL) al terc-butil {[5-(2-amino-2-oxoetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,25 g; 0,59 mmol), y la mezcla fue agitada a la temperatura ambiente por 20 min. La mezcla de reacción fue vertida en carbonato de hidrógeno de sodio acuoso saturado, y la mezcla se extrajo con acetato de etilo-tetrahidrofurano. El extracto fue secado sobre

sulfato de magnesio anhidro, y el solvente fue evaporado bajo presión reducida. Fue agregado 4N solución cloruro hidrógeno 1,4-dioxano (4 mL, 16 mmol) al residuo, y el solvente fue evaporado bajo presión reducida. El residuo fue lavado con diisopropil éter para dar dihidrocloruro de 2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetamido (0.19 g, rendimiento 81%) como un polvo blanco. ^{1}H-RMN (CD_3OD) δ:1,09-1,13 (6H; m); 2,09-2,22 (1H; m); 2,46 (3H; s); 2,77-2,80 (3H; m); 3,00-3,09 (2H; m); 3,51-3,55 (2H; m); 4,08(2H; brs); 7,15-7,22 (2H; m); 7,47(2H; d; J = 8,1Hz).

Ejemplo 7

Dihidrocloruro de metil [5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato

1) A una solución de terc-butil {[5-(cianometil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,90 g; 2,2 mmol) en etanol (20 mL) fue agregado 2N solución de hidróxido de sodio acuosa (5,5 mL; 11 mmol), y la mezcla fue calentada bajo reflujo durante 1,5 días. Fue agregado 6N ácido clorhídrico para acidificar la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto fue lavado con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue disuelto en N,N-dimetilformamida (5 mL). Fue agregado ioduro de metilo (0,65 g; 4,4 mmol) y carbonato de potasio (0,61 g; 4,4 mmol) a la

misma, y la mezcla fue agitada a la temperatura ambiente por 1 hr. Fue agregado acetato de etilo a la mezcla de reacción, y la mezcla fue lavada consecutivamente con agua y solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar metil [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (0,097 g; rendimiento 10%) como un aceite.

^{1}H-RMN ($CDCl_3$) δ:0.97 (6H, d, J = 6.6 Hz), 1.38 (9H, s), 2.13-2.28 (1H, m), 2.40 (3H, s), 2.49 (3H, s), 2.75 (2H, d, J = 7.4 Hz), 3.36 (2H, s), 3.61 (3H, s), 4.04-4.05 (2H, m), 4.27 (1H, brs), 6.98 (2H, d, J = 7.8 Hz), 7.23 (2H, d, J = 7.8 Hz).

2) Dihidrocloruro de metil [5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (0,069 g; rendimiento 76%) fue obtenido como polvo blanco de metil [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (0,097 g, 0,22 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (CD_3OD) δ:1,09-1,13 (6H; m); 2,12-2,26 (1H; m); 2,47 (3H; s); 2,84 (3H; s); 3,12 (2H; d; J = 7,4 Hz); 3,29-3,31 (2H; m); 3,63 (3H; s); 4,08 (2H; s); 7,19 (2H; d; J = 7,7

Hz); 7,48 (2H; d; J = 7,7 Hz).

Ejemplo 8

Etil (2E)-3-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acrilato

1) A una solución de terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,95 g; 4,9 mmol) en tetrahidrofurano (50 mL) fue agregado dióxido de manganeso (4,9 g; 56 mmol), y la mezcla fue agitada a temperatura ambiente por 19 hrs. La mezcla de reacción fue filtrada y el filtrado fue concentrado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice para dar terc-butil {[5-formil-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,25 g; rendimiento 65%) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,21-2,35 (1H; m); 2,43 (3H; s); 2,79 (3H; s); 2,82 (2H; d; J = 7,2 Hz); 4,15 (2H; d; J = 4,9 Hz); 4,38 (1H; brs); 7,10 (2H; d; J = 8,1 Hz); 7,29 (2H; d; J = 8,1 Hz); 9,71 (1H; s).

2) A una solución de fosfonoacetato de trietilo (0,033 g; 1,5 mmol) en tetrahidrofurano (10 mL) fue agregado hidruro de sodio (60% en aceite; 0,060 g; 1,5 mmol) a 0°C, y la mezcla fue agitada por 20 min. Una solución de terc-butil {[5-formil-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,38 g; 0,98 mmol) en tetrahidrofurano (5

mL) fue agregado a la mezcla de reacción, y la mezcla fue agitada a temperatura ambiente por 45 min. Fue agregado acetato de etilo a la mezcla de reacción, y la mezcla fue lavada consecutivamente con solución salina saturada, solución de cloruro de amonio acuosa saturada y solución salina saturada, y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar etil (2E)-3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acrilato (0,44 g; rendimiento 96%) como un aceite.

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,23 (3H; t; J = 7,2 Hz); 1,39 (9H; s); 2,16-2,27 (1H; m); 2,40 (3H; s); 2,64 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 4,08-4,17 (4H; m); 4,21 (1H; brs); 5,76 (1H; d; J = 16,4 Hz); 6,95 (2H; d; J = 8,1 Hz); 7,23 (2H; d; J = 8,1 Hz); 7,37 (1H; d; J = 16,4 Hz).

3) Una mezcla de etil (2E)-3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acrilato (0,12 g; 0,25 mmol) y 4N solución de cloruro de hidrógeno 1,4-dioxano (5 mL, 20 mmol) fueron agitados a temperatura ambiente por 10 min. El solvente fue evaporado bajo presión reducida, y el residuo fue dividido entre acetato de etilo-tetrahidrofurano y carbonato hidrógeno de sodio acuoso saturado. La capa

orgánica y fue combinado con un extracto obtenido extrayendo la capa acuosa con acetato de etilo-tetrahidrofurano, y la mezcla fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida, y el residuo fue purificado por cromatografía en columna de gel de sílice para dar etil (2E)-3-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acrilato (0,059 g, rendimiento 64%).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,23 (3H; t; J = 7,2 Hz); 1,30 (2H; brs); 2,18-2,33 (1H; m); 2,40 (3H; s); 2,63 (3H; s); 2,79 (2H; d; J = 7,1 Hz); 3,60 (2H; s); 4,13 (2H; q; J = 7,2 Hz); 5,76 (1H; d; J = 16,4 Hz); 7,01 (2H; d; J = 8,0 Hz); 7,24 (2H; d; J = 8,0 Hz); 7,39 (1H; d; J = 16,4 Hz).

Ejemplo 9

Dihidrocloruro de ácido (2E)-3-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acrílico

1) A una solución de etil (2E)-3-[5-({[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acrilato (0,32 g; 0,69 mmol) en tetrahidrofurano (10 mL) fue agregado 1N solución de hidróxido de sodio acuosa (3,4 mL; 3,4 mmol), y la mezcla fue agitada a 60°C por 12 hrs. La mezcla de reacción fue acidificada con 1N ácido clorhídrico y fue extraída con acetato de etilo. Los extractos fueron combinados, y la mezcla fue lavada con solución salina saturada y fue secada

sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar ácido (2E)-3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acrílico (0,28 g; rendimiento 93%) como un sólido blanco.

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,4 Hz); 1,39 (9H; s); 2,10-2,20 (1H; m); 2,39 (3H; s); 2,64 (3H; s); 2,79 (2H; d; J = 7,2 Hz); 4,00-4,20 (2H; m); 4,34 (1H; brs); 5,76 (1H; d; J = 16,4 Hz); 6,97 (2H; d; J = 7,5 Hz); 7,22 (2H; d; J = 7,5 Hz); 7,41 (1H; d; J = 16.4 Hz).

2) . Dihidrocloruro de ácido (2E)-3-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acrílico (0,077 g; rendimiento 90%) fue obtenido como polvo blanco de (2E)-3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acrílico el ácido (0.093 g, 0.21 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (CD_3OD) δ:1,10 (6H; d; J = 6,6 Hz); 2,12-2,27 (1H; m); 2,46 (3H; brs); 2,84 (3H; s); 3,05 (2H; d; J = 7,5 Hz); 4,13 (2H; s); 5,98 (1H; d; J = 16,3 Hz); 7,20 (2H; d; J = 8,0 Hz); 7,25 (1H; d; J = 16,3 Hz); 7,46 (2H; d; J = 8,0 Hz).

Ejemplo 10

Dihidrocloruro de (2E)-3-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acrilamida

1) Terc-butil {[5-[(1E)-3-amino-3-oxoprop-1-en-1-il]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,19 g, rendimiento 99%) se obtuvo de ácido (2E)-3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acrílico (0,19 g; 0,43 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN (CD_3OD) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,09-2,20 (1H; m); 2,37 (3H; s); 2,59 (3H; s); 2,74 (2H; d; J = 7,2 Hz); 3,99 (2H; s); 4,34 (1H; brs); 6,00 (1H; d; J = 16,2 Hz); 7,06 (2H; d; J = 8,1 Hz); 7,22-7,28 (3H; m).

2) Dihidrocloruro de (2E)-3-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acrilamida (0,078 g; rendimiento 99%) se obtuvo de terc-butil {[5-[(1E)-3-amino-3-oxoprop-1-en-1-il]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,083 g; 0,19 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (CD_3OD) δ:1,11 (6H; d; J = 6,6 Hz); 2,13-2,22 (1H; m); 2,45 (3H; s); 2,87 (3H; s); 3,10 (2H; d; J = 7,5 Hz); 4,15 (2H; s); 6,12 (1H; d; J = 16,2 Hz); 7,11 (1H; d; J = 16,2 Hz); 7,23 (2H; d; J = 7,9 Hz); 7,45 (2H; d; J = 7,9 Hz).

Ejemplo 11

Metil 5-(aminometil)-6-isobutil-2-metil-4-fenilnicotinato

1) Metil 5-ciano-6-isobutil-2-metil-4-fenil-1,4-dihidropiridin-3-carboxilato (10,7 g; rendimiento 86%) fue

obtenido como polvo blanco de 5-metil-3-oxohexannitrilo (5,0 g; 40 mmol), benzaldehído (4,2 g; 40 mmol) y metil 3-aminocrotonato (4,6 g; 40 mmol) según un método similar al método del Ejemplo 1-2).

^{1}H-RMN ($CDCl_3$) δ:0,93 (3H; d; J = 6,6 Hz); 0,99 (3H; d; J = 6,6 Hz); 1,82-1,97 (1H; m); 2,18-2,34 (2H; m); 2,38 (3H; s); 3,57 (3H; s); 4,61 (1H; s); 5,69 (1H; brs); 7,18-7,32 (5H; m).

2) Metil 5-ciano-6-isobutil-2-metil-4-fenilnicotinato (8,4 g; rendimiento 80%) fue obtenido como polvo blanco de metil 5-ciano-6-isobutil-2-metil-4-fenil-1,4-dihidropiridin-3-carboxilato (10,7 g; 34 mmol) según un método similar al método del Ejemplo 1-3).

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,8 Hz); 2,21-2,35 (1H; m); 2,64 (3H; s); 2,96 (2H; d; J = 7,2 Hz); 3,57 (3H; s); 7,33-7,39 (2H; m); 7,44-7,50 (3H; m).

3) Metil 5-(aminometil)-6-isobutil-2-metil-4-fenilnicotinato (0,21 g; rendimiento 2,5%) fue obtenido como polvo blanco metil 5-ciano-6-isobutil-2-metil-4-fenilnicotinato (8,4 g; 27 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:1,02 (6H; d; J = 6,6 Hz); 2,17-2,33 (1H; m); 2,54 (3H; s); 2,81 (2H; d; J = 7,4 Hz); 3,46 (3H; s); 3,65 (2H; s); 7,20-7,25 (2H; m); 7,38-7,46 (3H; m).

Ejemplo 12

metil 5-(aminometil)-6-isobutil-4-(4-metilfenil)-2-propilnicotinato

1) Una mezcla de metil 3-oxohexanoato (7,2 g; 50 mmol), acetato de amonio (19,3 g; 250 mmol), ácido acético (3,0 g; 50 mmol) y tolueno (500 mL) fue calentada bajo reflujo usando una trampa Dean-Stark por 11 hrs. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo fue dividido entre acetato de etilo y solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro, y el solvente fue evaporado bajo presión reducida para dar metil 3-aminohex-2-enoato como un aceite incoloro.

Metil 5-ciano-6-isobutil-4-(4-metilfenil)-2-propil-1,4-dihidropiridin-3-carboxilato (11,8 g; rendimiento 84%) se obtuvo como un aceite de 5-metil-3-oxohexannitrilo (5,0 g; 40 mmol), p-tolualdehído (4,8 g; 40 mmol) y el aceite incoloro mencionado precedentemente de metil 3-aminohex-2-enoato, según un método similar al método del Ejemplo 1-2).

^{1}H-RMN ($CDCl_3$) δ:0,93-1,05 (6H; m); 1,26 (3H; q; J = 7,2 Hz); 1,59-1,69 (2H; m); 1,83-1,96 (1H; m); 2,23-2,47 (2H; m); 2,30 (3H; s); 2,69-2,74 (2H; m); 3,57 (3H; s); 4,58 (1H; s); 5,65 (1H; brs); 7,09 (2H; d; J = 8,1 Hz); 7,13 (2H; d; J = 8,1 Hz).

2) Metil 5-ciano-6-isobutil-4-(4-metilfenil)-2-propilnicotinato (9,4 g; rendimiento 80%) se obtuvo como un

aceite de metil 5-ciano-6-isobutil-4-(4-metilfenil)-2-propil-1,4-dihidropiridin-3-carboxilato (11,8 g; 33 mmol) según un método similar al método del Ejemplo 1-3).

^{1}H-RMN ($CDCl_3$) δ:0,98 (3H; t; J = 7,4 Hz); 1,01 (6H; d; J = 6,6 Hz); 1,73-1,85 (2H; m); 2,22-2,35 (1H; m); 2,41 (3H; s); 2,78 (2H; m); 2,96 (2H; d; J = 7,4 Hz); 3,58 (3H; s); 7,23-7,32 (4H; m).

3) Metil 5-(aminometil)-6-isobutil-4-(4-metilfenil)-2-propilnicotinato (0,78 g; rendimiento 88%) se obtuvo como un aceite de metil 5-ciano-6-isobutil-4-(4-metilfenil)-2-propilnicotinato (0,88 g; 2,6 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,94-0,99 (9H; m); 1,70-1,83 (2H; m); 2,18-2,31 (1H; m); 2,39 (3H; s); 2,69-2,74 (2H; m); 2,81 (2H; d; J = 7,2 Hz); 3,48 (3H; s); 3,65 (2H; s); 7,12 (2H; d; J = 8,1 Hz); 7,21 (2H; d; J = 8,1 Hz).

Ejemplo 13

Dihidrocloruro de ácido [5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acético

1) A una solución de metil [5-({[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (0,25 g; 0,56 mmol) en tetrahidrofurano (15 mL) fue agregado etanol (10 mL) y 8N solución de hidróxido de sodio acuosa (3,0 mL; 24 mmol), y la

mezcla fue calentada bajo reflujo por 3 hrs. La mezcla de reacción fue acidificada con 6N ácido clorhídrico y fue extraída con acetato de etilo. El extracto fue lavado con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida, y el residuo fue purificado por cromatografía en columna de gel de sílice para dar el ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acético (0,16 g; rendimiento 65%) como un polvo blanco.

2) Dihidrocloruro de ácido [5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acético (0.15 g, rendimiento 99%) fue obtenido como polvo blanco del ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acético (0,16 g; 0.36 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (CD_3OD) δ:1,10 (6H; d; J = 6,4 Hz); 2,09-2,25 (1H; m); 2,48 (3H; s); 2,84 (3H; s); 3,10 (2H; d; J = 7,4 Hz); 3,60 (2H; s); 4,09 (2H; s); 7,20 (2H; d; J = 7,9 Hz); 7,49 (2H; d; J = 7,9 Hz).

Ejemplo 14

Metil 5-(aminometil)-6-isobutil-2-(2-metoxi-2-oxoetil)-4-(4-metilfenil)nicotinato

1) Dimetil 3-aminopent-2-enedioato se obtuvo de dimetil 1,3-acetonedicarboxilato (7,0 g; 40 mmol) según un método

similar al método del Ejemplo 12-1).

Metil 5-ciano-6-isobutil-2-(2-metoxi-2-oxoetil)-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (11,5 g; rendimiento 75%) se obtuvo como un aceite amarillo del dimetil 3-aminopent-2-endioato obtenido, 5-metil-3-oxohexannitrilo (5,0 g; 40 mmol) y p-tolualdehído (4,8 g; 40 mmol).

^{1}H-RMN ($CDCl_3$) δ:0,94 (3H; d; J = 6,6 Hz); 0,98 (3H; d; J = 6,6 Hz); 1,85-2,00 (1H; m); 2,20-2,40 (2H; m); 2,31 (3H; s); 3,58 (3H; s); 3,77 (3H; s); 3,85-4,10 (2H; m); 4,59 (1H; s); 7,01 (1H; brs); 7,10 (2H; d; J = 8,1 Hz); 7,16 (2H; d; J = 8,1 Hz).

2) Metil 5-ciano-6-isobutil-2-(2-metoxi-2-oxoetil)-4-(4-metilfenil)nicotinato (3,2 g; rendimiento 28%) se obtuvo como aceite amarillo-naranja de metil 5-ciano-6-isobutil-2-(2-metoxi-2-oxoetil)-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (11,5 g; 30 mmol) según un método similar al método de Ejemplo 1-3).

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,6 Hz); 2,20-2,35 (1H; m); 2,41 (3H; s); 2,97 (2H; d; J = 7,2 Hz); 3,54 (3H; s); 3,71 (3H; s); 4,04 (2H; s); 7,20-7,30 (4H; m).

3) Metil 5-(aminometil)-6-isobutil-2-(2-metoxi-2-oxoetil)-4-(4-metilfenil)nicotinato (2,5 g; rendimiento 77%) se obtuvo como un aceite amarillo pálido de metil 5-ciano-6-isobutil-2-

(2-metoxi-2-oxoetil)-4-(4-metilfenil)nicotinato (3,2 g; 8,4 mmol) según un método similar al método de Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,8 Hz); 1,39 (2H; brs); 2,15-2,35 (1H; m); 2,39 (3H; s); 2,82 (2H; d; J = 7,4 Hz); 3,45 (3H; s); 3,67 (2H; s); 3,70 (3H; s); 3,94 (2H; s); 7,05-7,25 (4H; m).

Ejemplo 15

Metil 5-(aminometil)-4-(2,6-difluorofenil)-6-isobutil-2-metilnicotinato

1) Metil 5-ciano-4-(2,6-difluorofenil)-6-isobutil-2-metil-1,4-dihidropiridin-3-carboxilato (14,8 g; rendimiento 36%) se obtuvo como cristales amarillos de 5-metil-3-oxohexannitrilo (15,0 g; 120 mmol) y 2,6-difluorobenzaldehído (17,0 g; 120 mmol) y metil 3-aminocrotonato (13,8 g; 120 mmol) según un método similar al método de Ejemplo 1-2).

^{1}H-RMN ($CDCl_3$) δ:0,95-1,05 (6H; m); 1,80-2,05 (1H; m); 2,10-2,45 (2H; m); 2,31 (3H; s); 3,56 (3H; s); 5,21 (1H; s); 5,87 (1H; brs); 6,75-6,90 (2H; m); 7,05-7,25 (1H; m).

2) Metil 5-ciano-4-(2;6-difluorofenil)-6-isobutil-2-metilnicotinato (11,7 g; rendimiento 80%) se obtuvo como cristales amarillos de metil 5-ciano-4-(2,6-difluorofenil)-6-isobutil-2-metil-1,4-dihidropiridin-3-carboxilato (14,8 g; 43 mmol) según un método similar al método de Ejemplo 1-3).

^{1}H-RMN ($CDCl_3$) δ:1,15 (6H; d; J = 6,6 Hz); 2,15-2,40 (1H; m);

2,72 (3H; s); 2,97 (2H; d; J = 7,0 Hz); 3,65 (3H; s); 6,95-7,10 (2H; m); 7,35-7,55 (1H; m).

3) Metil 5-(aminometil)-4-(2,6-difluorofenil)-6-isobutil-2-metilnicotinato (9,8 g; rendimiento 83%) se obtuvo como sólido amarillo pálido de metil 5-ciano-4-(2,6-difluorofenil)-6-isobutil-2-metilnicotinato (11,7 g; 34 mmol) según un método similar al método de Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,51 (2H; brs); 2,15-2,35 (1H; m); 2,60 (3H; s); 2,83 (2H; d; J = 7,5 Hz); 3,56(3H; s); 3,62(2H; s); 6,95-7,05(2H; m); 7,35-7,50(1H; m).

Punto de fusión: 48-49°C

Ejemplo 16

Metil 5-(aminometil)-4-(4-fluorofenil)-6-isobutil-2-metilnicotinato

1) Metil 5-ciano-4-(4-fluorofenil)-6-isobutil-2-metil-1,4-dihidropiridin-3-carboxilato (27,4 g; rendimiento 70%) fue obtenido como un aceite amarillo de 5-metil-3-oxohexannitrilo (15,0 g; 120 mmol), 4-fluorobenzaldehído (14,9 g; 120 mmol) y metil 3-aminocrotonato (13,8 g; 120 mmol) según un método similar al método del Ejemplo 1-2).

2) Metil 5-ciano-4-(4-fluorofenil)-6-isobutil-2-metilnicotinato (24,0 g; rendimiento 61%) se obtuvo como un aceite amarillo de metil 5-ciano-4-(4-fluorofenil)-6-isobutil-2-metil-1,4-dihidropiridin-3-carboxilato (27 g, 82 mmol) según un método similar al método de Ejemplo 1-3).

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,6 Hz); 2,15-2,40 (1H; m); 2,64 (3H; s); 2,96 (2H; d; J = 7,2 Hz); 3,61 (3H; s); 7,10-7,40 (4H; m).

3) Metil 5-(aminometil)-4-(4-fluorofenil)-6-isobutil-2-metilnicotinato (11,2 g; rendimiento 85%) se obtuvo como un sólido amarillo pálido de metil 5-ciano-4-(4-fluorofenil)-6-isobutil-2-metilnicotinato (13,0 g; 40 mmol) según un método similar al método de Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,26 (2H; brs); 2,15-2,35 (1H; m); 2,54 (3H; s); 2,81 (2H; d; J = 7,2 Hz); 3,51 (3H; s); 3,65 (2H; s); 7,00-7,30 (4H; m).

Punto de fusión: 55-57°C

Ejemplo 17

Dihidrocloruro de ácido 5-(aminometil)-6-isobutil-4-(4-metilfenil)-2-propilnicotínico

1) Metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)-2-propilnicotinato (0,71 g; rendimiento 71%) se obtuvo como un sólido blanco de metil 5-(aminometil)-6-isobutil-4-(4-metilfenil)-2-propilnicotinato (0,78 g; 2,2 mmol) según un método similar al método de Ejemplo 2-1).

^{1}H-RMN ($CDCl_3$) δ:0,94-0,99 (9H; m); 1,39 (9H; s); 1,70-1,83 (2H; m); 2,16-2,27 (1H; m); 2,38 (3H; s); 2,70-2,75 (2H; m); 2,79 (2H; d; J = 7,2 Hz); 3,48 (3H; s); 4,14 (2H; d; J = 4,9 Hz); 4,24 (1H; brs); 7,06 (2H; d; J = 7,9 Hz); 7,20 (2H; d; J

= 7,9 Hz).

2) El ácido 5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)-2-propilnicotínico (0,59 g; rendimiento 86%) se obtuvo de metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)-2-propilnicotinato (0.71 g, 1.6 mmol) según un método similar al método de Ejemplo 2-2).

^{1}H-RMN ($CDCl_3$) δ:0,94-1,05 (9H; m); 1,39 (9H; s); 1,72-1,84 (2H; m); 2,12-2,22 (1H; m); 2,38 (3H; s); 2,81-2,92 (4H; m); 4,40-4,09 (2H; m); 7,20 (2H; d; J = 8,3 Hz); 7,26 (2H; d; J = 8,3 Hz).

3) Dihidrocloruro de ácido 5-(Aminometil)-6-isobutil-4-(4-metilfenil)-2-propilnicotínico (0.50 g, rendimiento 90%) fue obtenido como polvo blanco de ácido 5-{[(terc-butoxicarbonil)amino]metil)-6-isobutil-4-(4-metilfenil)-2-propilnicotínico (0,59 g; 1,3 mmol) según un método similar al método de Ejemplo 2-3).

^{1}H-RMN (CD_3OD) δ:1,04-1,13 (9H; m); 1,76-1,91 (2H; m); 2,13-2,25 (1H; m); 2,44 (3H; s); 3,01-3,18 (4H; m); 4,20 (2H; brs); 7,28-7,36 (2H; m); 7,43 (2H; d; J = 7,9 Hz).

Ejemplo 18

Dihidrocloruro de ácido 5-(aminometil)-6-isobutil-2-metil-4-fenilnicotínico

1) Metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-fenilnicotinato (9,4 g; rendimiento 83%) se obtuvo

como un sólido blanco de metil 5-(aminometil)-6-isobutil-2-metil-4-fenilnicotinato (8,5 g; 27 mmol) según un método similar al método de Ejemplo 2-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,15-2,20 (1H; m); 2,55 (3H; s); 2,79 (2H; d; J = 7,2 Hz); 3,46 (3H; s); 4,14 (2H; d; J = 4,9 Hz); 4,24 (1H; brs); 7,14-7,21 (2H; m); 7,37-7,44 (3H; m).

2) El ácido 5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-fenilnicotínico (0.39 g, rendimiento 40%) se obtuvo como un sólido blanco de metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-fenilnicotinato (1,0 g; 2,4 mmol) según un método similar al método de Ejemplo 2-2).

3) Dihidrocloruro de ácido 5-(Aminometil)-6-isobutil-2-metil-4-fenilnicotínico (0.25 g, rendimiento 86%) fue obtenido como polvo blanco de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-fenilnicotínico (0,39 g; 0,98 mmol) según un método similar al método de Ejemplo 2-3).

^{1}H-RMN (CD_3OD) δ:1,04-1,15 (6H; m); 2,12-2,28 (1H; m); 2,78-2,89 (3H; m); 3,01-3,14 (2H; m); 4,13-4,20 (2H; m); 7,38-7,47 (2H; m); 7,56-7,63 (3H; m).

Ejemplo 19

Metil 5-[(dimetilamino)metil]-6-isobutil-2-metil-4-(4-

metilfenil)nicotinato

Una mezcla de metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,50 g, 1,6 mmol), ácido fórmico (5 mL) y formalina (5 mL) fueron agitados a 100°C por 12 hrs. La mezcla de reacción fue vertida en carbonato hidrógeno de sodio acuoso saturado, y la mezcla se extrajo con acetato de etilo. El extracto fue secado sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice para dar metil 5-[(dimetilamino)metil]-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,10 g; rendimiento 19%). ^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,8 Hz); 1,97 (6H; s); 2,14-2,28 (1H; m); 2,39 (3H; s); 2,53 (3H; s); 2,89 (2H; d; J = 7,4 Hz); 3,23 (2H; s); 3,48 (3H; s); 7,04 (2H; d; J = 8,0 Hz); 7,17 (2H; d; J = 8,0 Hz).

Ejemplo 20

Metil 5-(aminometil)-2-metil-6-isobutil-[4,4'-bipiridin]-3-carboxilato

1) Metil 5-ciano-6-isobutil-2-metil-1,4-dihidro-4,4'-bipiridin-3-carboxilato (26,4 g; rendimiento 71%) se obtuvo como un aceite amarillo de 5-metil-3-oxohexannitrilo (15,0 g; 120 mmol), isonicotinaldehído (12,8 g; 120 mmol) y metil 3-aminocrotonato (13,8 g; 120 mmol) según un método similar al método de Ejemplo 1-2).

2) A una solución de metil 5-ciano-6-isobutil-2-metil-1,4-

dihidro-4,4'-bipiridin-3-carboxilato (20 g, 64 mmol) en acetona (150 mL) fue agregado nitrato de cerio diamonio (45 g, 82 mmol), y la mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue enfriada a 0°C y fue dividida entre acetato de etilo y 2N hidróxido de sodio. Se combinaron la capa orgánica y un extracto obtenidos extrayendo la capa acuosa con acetato de etilo y la mezcla fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida, y el residuo fue purificado por cromatografía en columna de gel de sílice para dar metil 5-ciano-6-isobutil-2-metil-4,4'-bipiridin-3-carboxilato (10,2 g; rendimiento 51%) como un aceite amarillo.

3) Metil 5-(aminometil)-2-metil-6-isobutil-[4,4'-bipiridin]-3-carboxilato (10,9 g; rendimiento 72%) se obtuvo como sólido amarillo pálido de metil 5-ciano-6-isobutil-2-metil-4,4'-bipiridin-3-carboxilato (15,0 g; 48 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,33 (2H; brs); 2,15-2,40 (1H; m); 2,57 (3H; s); 2,82 (2H; d; J = 7,2 Hz); 3,49 (3H; s); 3,61 (2H; s); 7,15-7,25 (2H; m); 8,65-8,70 (2H; m).

Punto de fusión: 63-65°C

Ejemplo 21

Metil 5-(aminometil)-2-metil-4-(4-metilfenil)-6-

neopentilnicotinato

1) 5,5-dimetil-3-oxohexannitrilo (92.0g, rendimiento 99%) fue obtenido como un aceite de metil 3,3-dimetilbutanoato (86,0 g; 0.66 mol) según un método similar al método del Ejemplo 1-1).

^{1}H-RMN ($CDCl_3$) δ:1,05 (9H; s); 2,49 (2H; s), 3,43 (2H, s).

2) Una mezcla de 5,5-dimetil-3-oxohexannitrilo (22,0 g; 158 mmol), p-tolualdehido (19 g, 158 mmol), piperidina (1,3 g; 15,8 mmol), ácido acético (1,9 g; 31.6 mmol) y tolueno (300 mL) fueron calentados bajo reflujo por 12 hrs. usando una trampa Dean-Stark. Después de permitir que se enfríe a la temperatura ambiente, la mezcla de reacción fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue disuelto en metanol (50 mL). Metil 3-aminocrotonato (18,2 g; 158 mmol) fue agregado a los mismos y la mezcla fue calentada bajo reflujo por 6 hrs. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo fue purificado por cromatografía en columna de gel de sílice para dar metil 5-ciano-2-metil-4-(4-metilfenil)-6-neopentil-1,4-dihidropiridin-3-carboxilato (23 g, rendimiento 43%) como un aceite.

^{1}H-RMN ($CDCl_3$) δ:1,01 (9H; s); 0,98 (3H; d; J = 6,6 Hz); 1,80-2,00 (1H; m); 2,14-2,41 (2H; m); 2,31 (3H; s); 2;37 (3H; s);

3,58 (3H; s); 4,57 (1H; s); 5,56 (1H; brs); 7,06-7,16 (4H; m).

3) Metil 5-ciano-2-metil-4-(4-metilfenil)-6-neopentilnicotinato (12 g, rendimiento 60%) fue obtenido como cristales incoloros de metil 5-ciano-2-metil-4-(4-metilfenil)-6-neopentil-1,4-dihidropiridin-3-carboxilato (20 g, 59.4 mmol) según un método similar al método de Ejemplo 1-3).

^{1}H-RMN ($CDCl_3$) δ:1,06 (9H; s); 2,41 (3H; s); 2,63 (3H; s); 3,01 (2H; s); 3,61 (3H; s); 7,26 (4H; m).

Punto de fusión: 139-140°C

4) El metil 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotinato (2,3 g; rendimiento 56%) se obtuvo como cristales incoloros de metil 5-ciano-2-metil-4-(4-metilfenil)-6-neopentilnicotinato (4 g; 11,9 mmol) según un método similar al método de Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,44 (2H; brs); 2,39 (3H; s); 2,53 (3H; s); 2,88 (2H; s); 3,50 (3H; s); 3,72 (2H; s); 7,12 (2H; m); 7,21 (2H; m).

Punto de fusión: 119-120°C

Ejemplo 22

Dihidrocloruro de ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico

1) A una solución de metil 5-(aminometil)-2-metil-4-(4-

metilfenil)-6-neopentilnicotinato (1,0 g; 2,9 mmol) en tetrahidrofurano (25 mL) fue agregado dicarbonato de di-terc-butilo (0,65 g; 3,0 mmol), y la mezcla fue agitada a la temperatura ambiente por 1 hr. 8N solución de hidróxido de sodio acuosa (2 mL) y metanol (10 mL) se agregaaron a la mezcla de reacción, y la mezcla fue calentada bajo reflujo durante 3 días. La mezcla de reacción se permitió enfriarse a la temperatura ambiente, acidificado con 1N ácido clorhídrico, y fue extraída con acetato de etilo. El extracto fue lavado con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue cristalizado desde diisopropil éter para dar ácido 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilnicotinico (0,5 g; rendimiento 42%) como cristales.

^{1}H-RMN ($CDCl_3$) δ:0,88 (9H; s); 1,36 (9H; s); 2,38 (3H; s); 2,72 (3H; s); 2,88 (2H; s); 4,21 (2H; brs); 4,29 (1H; brs); 7,18 (2H; d; J = 8,3 Hz); 7,23 (2H; d; J = 8,3 Hz).

Punto de fusión: 216-217°C

2) Una solución 4N de cloruro de hidrógeno 1,4-dioxano (5 mL) fue agregado al ácido 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (0,30 g; 0,7 mmol), y la mezcla fue agitada a la temperatura ambiente por 17 hr. La mezcla de reacción fue concentrada bajo presión reducida y el sólido

blanco obtenido fue lavado con dietil éter para dar dihidrocloruro de ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (0,2 g; rendimiento 71%) como un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ:1,02 (9H; s); 2,37 (3H; s); 2,59 (3H; s); 3,04 (2H; s); 3,86 (2H; d; J = 5,5 Hz); 7,23 (2H; d; J = 8,1 Hz); 7,30 (2H; d; J = 8,1 Hz); 8,24 (3H; brs).

Ejemplo 23

Terc-butil 5-(aminometil)-4-(4-clorofenil)-6-isobutil-2-metilnicotinato

1) Una mezcla de acetoacetato de terc-butilo (580 mL; 3,5 mol), 25% de amonio acuoso (1200 mL) y metanol (1000 mL) fue agitado a temperatura ambiente por 14 hrs. Después de concentrarse bajo presión reducida, la mezcla de reacción fue dividida entre acetato de etilo y agua. La capa orgánica fue secada sobre sulfato de magnesio anhidro, y el solvente fue evaporado bajo presión reducida para dar terc-butil 3-aminocrotonato (550 g, rendimiento 99%) como un polvo amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ:1,47 (9H, s); 1,87 (3H; s); 4,46 (1H; s).

2) Terc-butil 4-(4-clorofenil)-5-ciano-6-isobutil-2-metil-1,4-dihidropiridin-3-carboxilato (7,6 g; rendimiento 62%) fue obtenido como polvo blanco de 5-metil-3-oxohexannitrilo (4,0 g; 32 mmol), 4-clorobenzaldehido (4,5 g; 32 mmol) y terc-

butil 3-aminocrotonato (5,0 g; 32 mmol) según un método similar al método de Ejemplo 1-2).

^{1}H-RMN ($CDCl_3$) δ:0,93 (3H; d; J = 6,6 Hz); 0,99 (3H; d; J = 6,6 Hz); 1,29 (9H; s); 1,80-1,95 (1H; m); 2,10-2,30 (2H; m); 2,34 (3H; s); 4,54 (1H; s); 5,56 (1H; brs); 7,10-7,20 (2H; m); 7,25-7,30 (2H; m).

Punto de fusión: 185-186°C

3) A una solución de terc-butil 4-(4-clorofenil)-5-ciano-6-isobutil-2-metil-1,4-dihidropiridin-3-carboxilato (7,6 g; 20 mmol) en acetona (200 mL) fue agregado una solución acuosa (40 mL) de nitrato de cerio diamonio (27 g, 49 mmol) a la temperatura ambiente durante 5 min. La mezcla de reacción fue dividida entre acetato de etilo y agua. Se combinaron la capa orgánica y un extracto obtenidos extrayendo la capa acuosa con acetato de etilo, y la mezcla fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar terc-butil 4-(4-clorofenil)-5-ciano-6-isobutil-2-metilnicotinato (7,2 g; rendimiento 95%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,8 Hz); 1,27 (9H; s); 2,15-2,35 (1H; m); 2,65 (3H; s); 2,94 (2H; d; J = 7,2 Hz); 7,30-7,35 (2H; m); 7,40-7,50 (2H; m).

Punto de fusión: 70-72°C

4) Una mezcla de terc-butil 4-(4-clorofenil)-5-ciano-6-isobutil-2-metilnicotinato (1,0 g; 2.6 mmol), Raney-cobalto (4 mL), 25% amonio acuoso (2 mL), tetrahidrofurano (20 mL) y metanol (40 mL) fue agitado en un tubo sellado bajo 5,098 kg/cm^2 de atmósfera de hidrógeno a la temperatura ambiente por 5 hrs. La mezcla de reacción fue filtrada y el filtrado fue concentrado bajo presión reducida. El residuo fue dividido entre acetato de etilo y 10% solución de carbonato de potasio acuosa. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar terc-butil 5-(aminometil)-4-(4-clorofenil)-6-isobutil-2-metilnicotinato (0,98 g; rendimiento 97%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,8 Hz); 1,22 (9H; s); 1,42 (2H; brs); 2,15-2,30 (1H; m); 2,55 (3H; s); 2,79 (2H; d; J = 7,2 Hz); 3,61 (2H; s); 7,21 (2H; d; J = 8,3 Hz); 7,41 (2H; d; J = 8,3 Hz).

Punto de fusión: 81-83°C

Ejemplo 24

Hidrocloruro de ácido 5-(aminometil)-4-(4-clorofenil)-6-isobutil-2-metilnicotínico

1) Una mezcla de terc-butil 5-(aminometil)-4-(4-clorofenil)-6-isobutil-2-metilnicotinato (0,60 g; 1,5 mmol) y

ácido trifluoracético (4 mL) fueron agitados a 50°C por 4 hrs. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo fue disuelto en 1,4-dioxano (4 mL). 4N solución de cloruro de hidrógeno 1,4-dioxano (4 mL, 16 mmol) fue agregado a la solución obtenida, y la mezcla se concentró bajo presión reducida. El residuo fue lavado con diisopropil éter para dar dihidrocloruro de ácido 5-(aminometil)-4-(4-clorofenil)-6-isobutil-2-metilnicotínico (0,63 g, rendimiento 99%) como un aceite incoloro.

2) Dihidrocloruro de ácido 5-(Aminometil)-4-(4-clorofenil)-6-isobutil-2-metilnicotínico (0,63 g; 1,5 mmol) fue disuelto en el isopropanol (10 mL), y óxido de propileno (0,27 g; 4,6 mmol) fue agregado a la misma. La mezcla fue agitada a la temperatura ambiente por 3 hrs. La mezcla de reacción fue concentrada bajo presión reducida, y el aceite obtenido se cristalizó del diisopropil éter - isopropanol para dar hidrocloruro de ácido 5-(aminometil)-4-(4-clorofenil)-6-isobutil-2-metilnicotínico (0,43 g; 76%) como un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,15-2,30 (1H; m); 2,49 (3H; s); 2,78 (2H; d; J = 7,2 Hz); 3,75 (2H; s); 7,34 (2H; d; J = 7,5 Hz); 7,54 (2H; d; J = 7,5 Hz); 8,43 (1H; brs).

Ejemplo 25

Terc-butil 5-(aminometil)-6-isobutil-2-isopropil-4-(4-

metilfenil)nicotinato

1) A una solución de ácido de Meldrum (14,41 g; 0,1 mol) y piridina (16,2 mL; 0,2 mol) en diclorometano (100 mL) fue agregado cloruro de isobutirilo por gotas (13,4 mL; 0,11 mol) a 0°C durante 30 min., y la mezcla fue agitada a 0°C por 2 hrs. La mezcla de reacción fue vertida en 0,5N ácido clorhídrico, y la mezcla se extrajo con diclorometano. El extracto fue lavado con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida. Una mezcla del residuo obtenido, terc-butanol (11,2 g; 150 mmol) y tolueno (100 mL) fue calentada bajo reflujo por 6 hrs. Después de permitir que se enfríe a la temperatura ambiente, la mezcla de reacción fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida para dar terc-butil 4-metil-3-oxopentanoato como un producto en bruto (9,31 g). Una mezcla del producto en bruto (9,31 g), 25% amonio acuoso (100 mL) y metanol (100 mL) fue agitada a temperatura ambiente por 12 hrs. La mezcla de reacción fue concentrada bajo presión reducida, y fue dividida entre acetato de etilo y agua. La capa orgánica fue secada sobre sulfato de magnesio anhidro, y el solvente fue evaporado bajo presión reducida para dar terc-butil 3-amino-4-metilpent-2-enoato como un producto en bruto (9,26 g).

2) El terc-butil 5-ciano-6-isobutil-2-isopropil-4-(4-

metilfenil)-1,4-dihidropiridin-3-carboxilato (12,11 g; rendimiento 76%) fue obtenido como cristales incoloros de 5-metil-3-oxohexannitrilo (5,0 g; 40 mmol), p-tolualdehído (4,8 g; 40 mmol) y el producto en bruto (9,26 g) de terc-butil 3-amino-4-metilpent-2-enoato que fue obtenido en el mencionado 1), según un método similar al método del Ejemplo 1-2).

3) El terc-butil 5-ciano-6-isobutil-2-isopropil-4-(4-metilfenil)nicotinato (2,88 g, rendimiento 73%) fue obtenido como un aceite de terc-butil 5-ciano-6-isobutil-2-isopropil-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (3,94 g; 10 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,6 Hz); 1,25 (9H; s); 1,32 (6H; d; J = 6,6 Hz); 2,26-2,35 (1H; m); 2,40 (3H; s); 2,94 (2H; d; J = 7,2 Hz); 3,14-3,23 (1H; m); 7,26-7,35 (4H; m).

4) El terc-butil 5-(aminometil)-6-isobutil-2-isopropil-4-(4-metilfenil)nicotinato (2,15 g, rendimiento 77%) fue obtenido como polvo blanco de terc-butil 5-ciano-6-isobutil-2-isopropil-4-(4-metilfenil)nicotinato (2,74 g; 7 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,18 (9H; s); 1,30 (6H; d; J = 6,6 Hz); 1,39 (2H; brs); 2,26-2,35 (1H; m); 2,39 (3H; s); 2,78 (2H; d; J = 6,9 Hz); 3,04-3,14 (1H; m); 3,60 (2H; s); 7,13 (2H; d; J = 8,2 Hz); 7,20 (2H; d; J = 8,2 Hz).

Ejemplo 26

Dihidrocloruro de ácido 5-(aminometil)-6-isobutil-2-isopropil-4-(4-metilfenil)nicotínico

Dihidrocloruro de ácido 5-(aminometil)-6-isobutil-2-isopropil-4-(4-metilfenil)nicotínico (0,37 g; rendimiento 90%) fue obtenido como polvo blanco de terc-butil 5-(aminometil)-6-isobutil-2-isopropil-4-(4-metilfenil)nicotinato (0,40 g; 1 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 1,03 (6H; d; J = 6,6 Hz); 2,23-2,37 (4H; m); 2,85 (2H; d; J = 6,9 Hz); 3,04-3,13 (1H; m); 3,77 (2H; d; J = 5,4 Hz); 7,22 (2H; d; J = 8,1 Hz); 7,28 (2H; d; J = 8,1 Hz); 8,21 (3H; brs).

Ejemplo 27

Terc-butil 5-(aminometil)-4-(4-clorofenil)-2-metil-6-neopentilnicotinato

1) Terc-butil 4-(4-clorofenil)-5-ciano-2-metil-6-neopentil-1,4-dihidropiridin-3-carboxilato (2,5 g; rendimiento 38%) fue obtenido como polvo blanco de 5,5-dimetil-3-oxohexannitrilo (2,6 g; 18,0 mmol), 4-clorobenzaldehído (2,3 g; 16,0 mmol) y terc-butil 3-aminocrotonato (2,5 g; 16,0 mmol) según un método similar al método del Ejemplo 1-2).

^{1}H-RMN ($CDCl_3$) δ:1,01 (9H; s); 1,29 (9H; s); 2,17 (1H; d; J = 13,9 Hz); 2,34 (3H; s); 2,35 (1H; d; J = 13,9 Hz); 4,55 (1H; s); 5,46 (1H; brs); 7,10-7,35 (4H; m).

Punto de fusión: 208-210°C

2) Terc-butil 4-(4-clorofenil)-5-ciano-2-metil-6-neopentilnicotinato (2,1 g; rendimiento 90%) fue obtenido como polvo amarillo pálido de terc-butil 4-(4-clorofenil)-5-ciano-2-metil-6-neopentil-1,4-dihidropiridin-3-carboxilato (2,4 g; 5,9 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,06 (9H; s); 1,28 (9H; s); 2,65 (3H; s); 3,00 (2H; s); 7,30-7,35 (2H; m); 7,45-7,50 (2H; m).

Punto de fusión: 94-95°C

3) Terc-butil 5-(aminometil)-4-(4-clorofenil)-2-metil-6-neopentilnicotinato (0,93 g; rendimiento 92%) fue obtenido como polvo blanco de terc-butil 4-(4-clorofenil)-5-ciano-2-metil-6-neopentilnicotinato (1,0 g; 2,5 mmol) según un método similar al método del Ejemplo 23-4).

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,22 (9H; s); 1,43(2H; brs); 2,55 (3H; s); 2,86 (2H; s); 3,66 (2H; s); 7,15-7,25 (2H; m); 7,35-7,45 (2H; m).

Punto de fusión: 116-118°C

Ejemplo 28

Dihidrocloruro de ácido 5-(aminometil)-4-(4-clorofenil)-2-metil-6-neopentilnicotínico

Dihidrocloruro de ácido 5-(Aminometil)-4-(4-clorofenil)-2-metil-6-neopentilnicotínico (1,0 g; rendimiento 98%) fue

obtenido como polvo blanco de terc-butil 5-(aminometil)-4-(4-clorofenil)-2-metil-6-neopentilnicotinato (0,95 g; 2.4 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:1,02 (9H; s); 2,56 (3H; s); 2,94 (2H; s); 3,84 (2H; d; J = 5,5 Hz); 7,35-7,40 (2H; m); 7,55-7,60 (2H; m); 8,20 (3H; brs).

Punto de fusión: 246-248°C

Ejemplo 29

Terc-butil 5-(aminometil)-4-(4-clorofenil)-2,6-dineopentilnicotinato

1) A una solución (30 mL) de piperidina (0,94 g; 11 mmol) y ácido acético (0,66 g; 11 mmol) en isopropanol por gotas fue agregada una solución (300 mL) de 5,5-dimetil-3-oxohexannitrilo (17,0 g; 110 mmol) y p-clorobenzaldehído (15,5 g; 110 mmol) en isopropanol a la temperatura ambiente durante 30 min. y la mezcla fue agitada durante 3 días. El solvente fue evaporado bajo presión reducida, y el residuo fue dividido entre acetato de etilo y la solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente evaporado bajo presión reducida para dar 3-(4-clorofenil)-2-(3,3-dimetilbutanoil)acrilonitrilo como un producto en bruto (35,2 g).

2) Terc-butil 3-amino-5,5-dimetilhex-2-enoato fue obtenido como un producto en bruto (13 g) de ácido de Meldrum (8,65 g;

60 mmol) y cloruro de terc-butilacetilo (9,2 mL; 66 mmol) según un método similar al método del Ejemplo 25-1).

3) Terc-butil 4-(4-clorofenil)-5-ciano-2,6-dineopentil-1,4-dihidropiridin-3-carboxilato (2,03 g; rendimiento 15%) se obtuvo como un aceite amarillo de producto en bruto (11,7 g) que se obtuvo en 1 mencionado precedentemente), y el producto en bruto (13,0 g) que fue obtenido en el 1 mencionado precedentemente), según un método similar al método del Ejemplo 1-2). Es decir, se disolvieron los dos tipos de productos crudos mencionados en metanol (40 mL) y la mezcla fue calentada bajo reflujo por 3,5 hrs. La mezcla de reacción fue concentrada bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar terc-butil 4-(4-clorofenil)-5-ciano-2,6-dineopentil-1,4-dihidropiridin-3-carboxilato.

^{1}H-RMN ($CDCl_3$) δ:1,00 (9H; s); 1,03 (9H; s); 1,29 (9H; s); 2,24 (4H; s); 4,58 (1H; brs); 5,37 (1H; brs); 7,20-7,32 (4H; m).

4) Terc-butil 4-(4-clorofenil)-5-ciano-2,6-dineopentilnicotinato (0,75 g; rendimiento 38%) se obtuvo de terc-butil 4-(4-clorofenil)-5-ciano-2,6-dineopentil-1,4-dihidropiridin-3-carboxilato (2,03 g; 4.44 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,04 (9H; s); 1,07 (9H; s); 1,24 (9H; s);

2,84 (2H; s); 3,00 (2H; s); 7,31 (2H; d; J = 8,67 Hz); 7,45 (2H; d; J = 8,67 Hz).

5) Terc-butil 5-(aminometil)-4-(4-clorofenil)-2,6-dineopentilnicotinato (0,35 g; rendimiento 46%) fue obtenido como un sólido amarillo pálido de terc-butil 4-(4-clorofenil)-5-ciano-2,6-dineopentilnicotinato (0,75 g; 1,65 mmol) según un método similar al método del Ejemplo 23-4).

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,04 (9H; s); 1,18 (9H; s); 2,74 (2H; s); 2,86 (2H; s); 3,64 (2H; s); 7,21 (2H; d; J = 8,48 Hz); 7,40 (2H; d; J = 8,48 Hz).

Ejemplo 30

Dihidrocloruro de ácido 5-(aminometil)-4-(4-clorofenil)-2,6-dineopentilnicotínico

El dihidrocloruro de ácido 5-(aminometil)-4-(4-clorofenil)-2,6-dineopentilnicotínico (0,21 g; rendimiento 69%) fue obtenido como un sólido blanco de terc-butil 5-(aminometil)-4-(4-clorofenil)-2,6-dineopentilnicotinato (0,30 g; 0,653 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (9H; s); 1,03 (9H; s); 2,77 (2H; s); 2,91 (2H; s); 3,83 (2H; d; J = 5,65 Hz); 7,35 (2H; d; J = 8,48 Hz); 7,54 (2H; d; J = 8,29 Hz); 8,12 (2H; brs).

Ejemplo 31

Hemifumarato de ácido 5-(aminometil)-2-metil-4-(4-

metilfenil)-6-neopentilnicotínico (a veces denominado fumarato de bis[ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico] en esta descripción)

1) A una mezcla de dihidrocloruro de ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (5,99 g; 15,0 mmol), tetrahidrofurano (50 mL) y 1M solución de hidróxido de sodio acuosa (50 mL) fue agregado cloroformato de bencilo por gotas (95%; 2,48 mL; 16,5 mmol) a temperatura ambiente. La mezcla obtenida fue agitada por 2 hrs., y fue agregado 0,1 M de ácido clorhídrico (100 mL). La mezcla se extrajo con acetato de etilo-tetrahidrofurano (1:1). La capa orgánica fue lavada con agua y solución salina saturada, fue secada sobre sulfato de magnesio anhidro y concentrada bajo presión reducida. El residuo fue recristalizado de tetrahidrofurano para dar ácido 5-({[(benciloxi)carbonil]amino}metil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (5,57 g; 81%) como cristales en polvo incoloros.

^{1}H-RMN (DMSO-d_6) δ:0,98 (9H; s); 2,33 (3H; s); 2,44 (3H; s); 2,70 (2H; s); 3,97 (2H; d; J = 4,1 Hz); 4,98 (2H; s); 7,15-7,20 (4H; m); 7,27-7,42 (6H; m); 12,96 (1H; brs).

2) Una mezcla de ácido 5-({[(benciloxi)carbonil]amino}metil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (5,5 g; 12 mmol), 5% paladio-carbono (11,0 g), tetrahidrofurano (100 mL) y etanol (100 mL) fueron agitados toda la noche bajo una atmósfera de hidrógeno a la

temperatura ambiente. La mezcla de reacción fue filtrada, y el filtrado fue concentrado bajo presión reducida. El residuo fue recristalizado desde metanol para dar ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (2,46 g; 63%) como cristales en polvo incoloros.

^{1}H-RMN (DMSO-d_6) δ:0,96 (9H; s); 2,33 (3H; s); 2,36 (3H; s); 2,76 (2H; s); 3,56 (2H; s); 7,12-7,18 (4H; m),

3) El ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (1,14 g; 3,50 mmol) y ácido fumárico (0,203 g; 1,75 mmol) fue disuelto en agua (150 mL) con calentamiento. La solución acuosa obtenida fue concentrada bajo presión reducida. El residuo fue lavado con etanol y recristalizado de agua para dar hemifumarate de ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (0,902 g; 67%) como cristales en polvo incoloros.

^{1}H-RMN (DMSO-d_6) δ:0,97 (9H; s); 2,34 (3H; s); 2,40 (3H; s); 2,77 (2H; s); 3,65 (2H; s); 6,45 (1H; s); 7,14-7,21 (4H; m).

Ejemplo 32

Terc-butil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) El terc-butil 5-ciano-6-isobutil-2-metil-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (159 g, rendimiento 27%) fue obtenido como un sólido blanco de terc-butil 3-aminocrotonato (253 g; 1,60 mol) según un método

similar al método del Ejemplo 1-2). A continuación, terc-butil 5-ciano-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (40,8 g; rendimiento 99%) fue obtenido como un sólido amarillo de terc-butil 5-ciano-6-isobutil-2-metil-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (41,0 g; 112 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,9 Hz); 1,26 (9H; s); 2,21-2,32 (1H; m); 2,41 (3H; s); 2,64 (3H; s); 2,93 (2H; d; J = 7,5 Hz); 7,18-7,32 (4H; m),

2) Terc-butil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (502 g, rendimiento 96%) fue obtenido como un sólido blanco de terc-butil 5-ciano-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (515 g; 1,42 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,19 (9H; s); 2,13-2,31 (1H; m); 2,39 (3H; s); 2,56 (3H; s); 2,79 (2H, d; J = 7,4 Hz); 3,64 (2H; brs); 7,13 (2H; d; J = 7,9 Hz); 7,22 (2H; d; J = 7,9 Hz).

Ejemplo 33

Dihidrocloruro de ácido ({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)acético

1) A una solución (10 mL) de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (510 mg; 1,24 mmol) en N,N-

dimetilformamida se agregaron bromoacetato de bencilo (568 mg; 2,48 mmol) y carbonato de potasio (343 mg; 2,48 mmol), y la mezcla fue agitada a la temperatura ambiente por 30 min. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar 2-(benciloxi)-2-oxoetil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (690 mg, rendimiento 99%) como un aceite.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,14-2,26 (1H; m); 2,36 (3H; s); 2,59 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 4,11-4,17 (2H; m); 4,22 (1H; brs); 4,40 (2H; s); 5,16 (2H; s); 7,05 (2H; d; J = 8,1 Hz); 7,17 (2H; d; J = 7,9 Hz); 7,29-7,39 (5H; m).

2) Una mezcla de 2-(benciloxi)-2-oxoetil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (690 mg; 1,23 mmol), paladio-carbono (10%, seco) (132 mg; 0,124 mmol) y etanol (10 mL) fue agitado bajo una atmósfera de hidrógeno a temperatura ambiente por 30 min. Después de filtración, el solvente fue evaporado bajo presión reducida para dar ácido ({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-

metilfenil)piridin-3-il]carbonil}oxi)acético como un producto en bruto (580 mg).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,37 (3H; s); 2,62 (3H; s); 2,81 (2H; d; J = 7,0 Hz); 4,11-4,17 (2H; m); 4,30 (1H; brs); 4,36 (2H; s); 7,06 (2H; d; J = 7,7 Hz); 7,19 (2H; d; J = 7,7 Hz).

3) Dihidrocloruro de ácido ({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)acético (517 mg, rendimiento 94%) fue obtenido como polvo blanco del producto en bruto (580 mg) que fue obtenido en el 2) mencionado precedentemente según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (CD_3OD) δ:1,11 (6H; d; J = 6,6 Hz); 2,15-2,27 (1H; m); 2,45 (3H; s); 2,94 (3H; s); 3,11 (2H; d; J = 7,5 Hz); 4,20 (2H; s); 4,50 (2H; s); 7,30 (2H; d; J = 8,1 Hz); 7,42 (2H; d; J = 7,9 Hz).

Ejemplo 34

2-Amino-2-oxoetil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) A una solución (10 mL) de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (500 mg; 1,22 mmol) en N,N-dimetilformamida se agregaron 2-iodoacetamida (673 mg; 3,64 mmol) y carbonato de potasio (337 mg; 2,44 mmol) y la mezcla

fue agitada a la temperatura ambiente por 30 min. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y lavada con una solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar 2-amino-2-oxoetil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (570 mg, rendimiento 99%) como un aceite.

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,17-2,31 (1H; m); 2,39 (3H; s); 2,57 (3H; s); 2,80 (2H; d; J = 7,2 Hz); 4,13-4,18 (2H; m); 4,23 (1H; brs); 4,40 (2H; s); 5,12 (2H; brs); 7,12 (2H; d; J = 7,7 Hz); 7,25 (2H; d; J = 7,9 Hz).

2) 2-Amino-2-oxoetil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (370 mg, rendimiento 82%) fue obtenido como un aceite de 2-amino-2-oxoetil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (570 mg; 1,21 mmol) según un método similar al método del Ejemplo 8-3).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 2,17-2,32 (1H; m); 2,40 (3H; s); 2,57 (3H; s); 2,82 (2H; d; J = 7,2 Hz); 3,70 (2H; s); 4,39 (2H; s); 5,20 (2H; brs); 7,19 (2H; d; J = 8,1 Hz); 7,27 (2H; d; J = 7,9 Hz).

Ejemplo 35

Dihidrocloruro de 4-etoxi-4-oxobutil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) Una mezcla de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (0,41 g, 1,0 mmol), etil 4-bromobutirato (0,21 g; 1,1 mmol), carbonato de potasio (0,15 g; 1,1 mmol) y N,N-dimetilformamida (20 mL) fueron agitados a temperatura ambiente por 1 hr., y la mezcla de reacción fue dividida entre acetato de etilo y agua. La capa orgánica fue lavada consecutivamente con agua y solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar 4-etoxi-4-oxobutil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,45 g; rendimiento 85%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,25 (3H; t; J = 7,2 Hz); 1,39 (9H; s); 1,55-1,70 (2H; m); 2,08 (2H; t; J = 7,5 Hz); 2,15-2,30 (1H; m); 2,38 (3H; s); 2,54 (3H; s); 2,78 (2H; d; J = 7,3 Hz); 3,95 (2H; t; J = 6,2 Hz); 4,11 (2H; q; J = 7,2 Hz); 4,53 (2H; d; J = 5,3 Hz); 4,23 (1H; brs); 7,07 (2H; d; J = 8,0 Hz); 7,21 (2H; d; J = 8,0 Hz).

2) Dihidrocloruro de 4-etoxi-4-oxobutil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,12 g;

rendimiento 95%) fue obtenido como polvo blanco de 4-etoxi-4-oxobutil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,13 g, 0,25 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 1,17 (3H; t; J = 7,2 Hz); 1,45-1,60 (2H; m); 2,05 (2H; t; J = 7,4 Hz); 2,15-2,30 (1H; m); 2,36 (3H; s); 2,51 (3H; brs); 2,85 (2H; t; J = 6,3 Hz); 3,82 (2H; d; J = 5,7 Hz); 3,92 (2H; t; J = 6,3 Hz); 4,03 (2H; q; J = 7,2 Hz); 7,19 (2H; d; J = 7,9 Hz); 7,28 (2H; d; J = 7,9 Hz); 8,21 (3H; brs).

Punto de fusión: 193-195°C

Ejemplo 36

Dihidrocloruro de ácido 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)butanoico

1) 4-Etoxi-4-oxobutil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,30 g, 0,57 mmol) fue disuelto en etanol (20 mL) y fue agregado 1N solución de hidróxido de sodio acuosa (4,0 mL). La mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue vertida en 0,5N ácido clorhídrico (20 mL) y la mezcla fue extractada con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y los cristales crudos obtenidos fueron recristalizados del acetato de etilo - diisopropil éter para

dar ácido 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)butanoico (0,23 g, rendimiento 82%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:1,02 (6H; d; J = 6,4 Hz); 1,39 (9H; s); 1,55-1,70 (2H; m); 2,12 (2H; t; J = 7,1 Hz); 2,15-2,30 (1H; m); 2,39 (3H; s); 2,75 (3H; brs); 2,85-3,20 (2H; m); 4,00 (2H; t; J = 6,2 Hz); 4,20 (2H; d; J = 3,6 Hz); 4,37 (1H; brs); 7,10 (2H; d; J = 7,7 Hz); 7,26 (2H; d; J = 7,7 Hz).

2) Dihidrocloruro de ácido 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)butanoico (0,20 g, rendimiento 99%) fue obtenido como polvo blanco de ácido 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)butanoico (0,20 g; 0,40 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 1,40-1,55 (2H; m); 2,00 (2H; t; J = 7,4 Hz); 2,15-2,30 (1H; m); 2,36 (3H; s); 2,52 (3H; brs); 2,80-2,95 (2H; m); 3,83 (2H; d; J = 4,3 Hz); 3,92 (2H; t; J = 6,2 Hz); 7,20 (2H; d; J = 7,7 Hz); 7,29 (2H; d; J = 7,7 Hz); 8,29 (3H; brs).

Punto de fusión: 221-223°C

Ejemplo 37

Trihidrocloruro de piridin-2-ilmetil 5-(aminometil)-6-

isobutil-2-metil-4-(4-metilfenil)nicotinato

1) A una solución (15 mL) de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,00 g; 2,42 mmol) en N,N-dimetilformamida se agregaron hidrobromuro de 2-(bromometil)piridina (0,92 g; 3,64 mmol) y carbonato de potasio (66,9 mg; 4,84 mmol), y la mezcla fue agitada por 30 min. La mezcla de reacción fue diluida con acetato de etilo (100 mL) y lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar piridin-2-ilmetil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,20 g; rendimiento 98%) como un sólido rosa pálido.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,14-2,25 (1H; m); 2,35 (3H; s); 2,56 (3H; s); 2,78 (2H; d; J = 7,2 Hz); 4,14 (2H; brs); 4,25 (1H; brs); 5,06 (2H; s); 6,89 (1H; d; J = 7,7 Hz); 7,06 (2H; d; J = 7,9 Hz); 7,13 (2H; d; J = 7,9 Hz); 7,17-7,22 (1H; m); 7,57 (1H; t, J = 7,7 Hz); 8,52 (1H; d; J = 4,7 Hz).

2) Trihidrocloruro de piridin-2-ilmetil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1.22 g, rendimiento 99%) fue obtenido como un sólido rosa pálido de

piridin-2-ilmetil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,20 g, 2,38 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,4 Hz); 2,17-2,28 (1H; m); 2,34 (3H; s); 2,61 (3H; s); 2,94 (2H; d; J = 6,8 Hz); 3,81 (2H; d; J = 4,9 Hz); 5,20 (2H; s); 7,19 (4H; s); 7,23 (1H; brs); 7,62-7,66 (1H; m); 8,06 (1H; t; J = 7,9 Hz); 8,39 (3H, brs), 8.68 (1H, d, J = 4.9 Hz).

Ejemplo 38

Dihidrocloruro de 2-etoxi-1-metil-2-oxoetil 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotinato

1) 2-Etoxi-1-metil-2-oxoetil 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilnicotinato (0,35 g; rendimiento 56%) fue obtenido como polvo blanco de ácido 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (0,5 g; 1,2 mmol) y etil 2-bromopropionato (0,43 g; 2,4 mmol) según un método similar al método del Ejemplo 33-1).

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,11 (3H; d; J = 7,0 Hz); 1,25 (3H; t; J = 7,1 Hz); 1,37 (9H; s); 2,38 (3H; s); 2,62 (3H; d; J = 4,9 Hz); 2,83-2,93 (2H; m); 4,17 (2H; q; J = 7,0 Hz); 4,21 (3H; s); 4,82 (1H; q; J = 7,1 Hz); 7,04-7,12 (2H; m); 7,19-7,21 (2H; m).

2) Dihidrocloruro de 2-Etoxi-1-metil-2-oxoetil 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotinato (0,16 g; rendimiento 85%) fue obtenido como polvo blanco de 2-etoxi-1-metil-2-oxoetil 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilnicotinato (0,2 g; 0,38 mmol) según un método similar al método del Ejemplo 22-2).

^{1}H-RMN (DMSO-d_6) δ:1,02 (9 H; s); 1,06 (3H; d; J = 7,0 Hz); 1,16 (3H; t; J = 7,1 Hz); 2,37 (3H; s); 2,58 (3H; s); 2,95 (2H; s); 3,88 (2H; s); 4,11 (2H; q; J = 7,0 Hz); 4,77 (1H; q; J = 7,1 Hz) 7,13-7,16 (1H; m); 7,23-7,32 (3H; m); 8,24 (3H; s).

Ejemplo 39

dihidrocloruro de (5-metil-2-oxo-1,3-dioxol-4-il)metil 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotinato

1) (5-metil-2-oxo-1,3-dioxol-4-il)metil 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilnicotinato (0,9 g; rendimiento 73%) fue obtenido como polvo blanco de ácido 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (1,0 g; 2.3 mmol) y 4-clorometil-5-metil-1,3-dioxol-2-ona (0,42 g; 2,8 mmol) según un método similar al método del Ejemplo 33-1).

^{1}H-RMN ($CDCl_3$) δ:1,01 (9H; s) 1,36 (9H; s); 1,97 (3H; s); 2,39

(3H; s); 2,53 (3H; s); 2,88 (2H; s); 4,16 (3H; s); 4,74 (2H; s); 7,02 (2H; d; J = 7,8 Hz); 7,17 (2H; d; J = 7,8 Hz).

2) A una solución (2 mL) de (5-metil-2-oxo-1,3-dioxol-4-il)metil 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilnicotinato (0,8 g; 1,5 mmol) en acetato de etilo fue agregado 4N solución ácido clorhídrico acetato de etilo (8 mL) y la mezcla fue agitada a la temperatura ambiente por 4 hrs. La mezcla de reacción fue concentrada bajo presión reducida y el sólido blanco obtenido fue recristalizado del metanol-acetato de etilo para dar dihidrocloruro de (5-metil-2-oxo-1,3-dioxol-4-il)metil 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotinato (0,6 g; rendimiento 77%) como un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ:1,00 (9H; s); 1,99 (3H; s); 2,34 (3H; s); 2,52 (3H; s); 2,93 (2H; s); 3,83 (2H; d; J = 5,5 Hz); 4,93 (2H; s); 7,13 (2H; d; J = 7,9 Hz); 7,20 (2H; d; J = 7,9 Hz; 1 H); 8,18 (3H; s).

Ejemplo 40

Hemifumarato de ácido 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (a veces denominado fumarato de bis[ácido 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico] en esta descripción)

1) Una solución mezcla de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (53,7 g; 130 mmol) y 4N solución de

ácido clorhídrico 1,4-dioxano (400 mL) fueron agitados a temperatura ambiente por 3 hrs. El sólido precipitado fue recolectado por filtración y lavado diisopropil éter (200 mL). El sólido blanco obtenido fue disuelto en isopropanol (500 mL) y la mezcla fue agitada a 50°C por 30 min. La mezcla obtenida se permitió enfriar a la temperatura ambiente, y la mezcla fue agitada a la temperatura ambiente por 1 hr. El sólido precipitado fue recolectado por filtración y lavado con isopropanol (50 mL) para dar solvato de propan-2-ol dihidrocloruro de ácido 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1:1) (46,5 g; rendimiento 80%) como un sólido blanco.

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 1,04 (6H; d; J = 6,0 Hz); 2,16-2,27 (1H; m); 2,37 (3H; s); 2,58 (3H; s); 2,90 (2H; d; J = 7,0 Hz); 3,73-3,86 (3H; m); 7,23 (2H; d; J = 8,1 Hz); 7,30 (2H; d; J = 7,9 Hz); 8,26 (3H; brs).

2) El solvato de propan-2-ol dihidrocloruro de ácido 5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1:1) (35,6 g; 80 mmol) fue suspendido en agua (80 mL) y 1N solución de hidróxido de sodio acuosa (160 mL, 160 mmol) fue agregada a la temperatura ambiente. La mezcla fue agitada por 1 hr. El sólido precipitado fue recolectado por filtración y lavado con etanol (10 mL) para dar ácido 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (13,3 g; rendimiento 53%) como un sólido blanco.

^{1}H-RMN (DMSO-d_6) δ:0,93 (6H; d; J = 6,8 Hz); 2,14-2,25 (1H; m); 2,34 (3H; s); 2,38 (3H; s); 2,70 (2H; d; J = 7,2 Hz); 3,49 (2H; s); 7,14-7,20 (4H; m),

3) El ácido 5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (15,4 g; 49.3 mmol) fue suspendido en agua (400 mL) y la mezcla fue calentada bajo reflujo con agitación durante 30 min. El ácido fumárico (3,43 g; 29,6 mmol) fue agregado a la suspensión obtenida y la mezcla fue agitada a la temperatura ambiente por 1 hr. El sólido precipitado fue recolectado por filtración y el filtrado fue lavado con agua (50 mL) para dar hemifumarato de ácido 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (13,9 g; rendimiento 76%) como cristales blancos.

^{1}H-RMN (DMSO-d_6) δ:0,93 (6H; d; J = 6,6 Hz); 2,26-2,28 (1H; m); 2,35 (3H; s); 2,42 (3H; s); 2,72 (2H; d; J = 7,2 Hz); 3,55 (2H; s); 6,49 (1H; s); 7,17 (2H; d; J = 8,3 Hz); 7,21 (2H; d; J = 8,3 Hz).

Ejemplo 41

Dihidrocloruro de 3-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]propionamida

Una mezcla de terc-butil {[5-[(1E)-3-amino-3-oxoprop-1-en-1-il]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (97,6 mg; 0,223 mmol), 10% paladio-carbono (24 mg; 0,0223 mmol) y etanol (5 mL) fue agitado bajo una

atmósfera de hidrógeno a temperatura ambiente por 16 hrs. Después de filtración, el solvente fue evaporado bajo presión reducida para dar terc-butil ([5-(3-amino-3-oxopropil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato como un producto en bruto. El producto en bruto fue disuelto en 4N solución cloruro de hidrógeno 1,4-dioxano (10 mL) y la mezcla fue agitada a temperatura ambiente por 30 min. El solvente fue evaporado bajo presión reducida y el sólido blanco obtenido fue lavado con diisopropil éter para dar dihidrocloruro de 3-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]propionamida (72.7 mg, rendimiento 79%) como un polvo blanco.

^{1}H-RMN (CD_3OD) δ:1,09 (6H; d; J = 6,2 Hz); 2,07-2,19 (1H; m); 2,24-2,29 (2H; m); 2,48 (3H; s); 2,84 (2H; t; J = 7,8 Hz); 2,90 (3H; s); 3,06 (2H; d; J = 7,7 Hz); 4,04 (2H; s); 7,29 (2H; d; J = 7,9 Hz); 7,50 (2H; d; J = 7,7 Hz).

Ejemplo 42

Dihidrocloruro de etil 3-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]propionato

1) Una mezcla de etil (2E)-3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acrilato (700 mg; 1,50 mmol), 10% paladio-carbono (160 mg; 0,15 mmol) y etanol (15 mL) fueron agitados bajo atmósfera de hidrógeno a la temperatura ambiente por 1 hr. Después de la filtración, el solvente fue

evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar etil 3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]propionato (480 mg, rendimiento 68%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,18 (3H; t; J = 7,2 Hz); 1,38 (9H; s); 2,11-2,30 (3H; m); 2,40 (3H; s); 2,57 (3H; s); 2,62-2,68 (2H; m); 2,72 (2H; d; J = 7,4 Hz); 3,96-4,07 (4H; m); 4,18 (1H; brs); 6,98 (2H; d; J = 7,91); 7,24 (2H; d; J = 7,9 Hz).

2) Dihidrocloruro de etil 3-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]propionato (58,3 mg; rendimiento 85%) fue obtenido como polvo blanco de etil 3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]propionato (73,0 mg; 0,156 mmol) según un método similar al método de Ejemplo 2-3).

^{1}H-RMN (CD_3OD) δ:1,08 (6H; d; J = 6,6 Hz); 1,17 (3H; t; J = 7,2 Hz); 2,08-2,21 (1H; m); 2,34-2,39 (2H; m); 2,48 (3H; s); 2,82-2,85 (2H; m); 2,88 (3H; s); 3,05 (2H; d; J = 7,5 Hz); 4,00-4,07 (4H; m); 7,27 (2H; d; J = 7,9 Hz); 7,50 (2H; d; J = 7,9 Hz).

Ejemplo 43

Dihidrocloruro de ácido 3-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]propiónico

1) A una solución mezcla (10 mL) de etil 3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]propionato (407 mg; 0,868 mmol) en tetrahidrofurano fue agregado 1N solución de hidróxido de sodio acuosa (4,30 mL; 4,30 mmol) y la mezcla fue agitada a 50°C por 5 hrs. La mezcla de reacción fue neutralizada con 6N ácido clorhídrico (0,8 mL) y fue extraída con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar ácido de 3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]propiónico (255 mg, rendimiento 60%) como un polvo amarillo.

^{1}H-RMN (CD_3OD) δ:1,04 (6H; d; J = 6,6 Hz); 2,05-2,17 (1H; m); 2,26-2,36 (2H; m); 2,44 (3H; s); 2,75-2,87 (5H; m); 2,97 (2H; d; J = 7,5 Hz); 4,05 (2H; s); 7,17 (2H; d; J = 8,1 Hz); 7,40 (2H; d; J = 7,7 Hz).

2) Dihidrocloruro de ácido 3-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]propiónico (94,2 mg, rendimiento 97%) fue obtenido como polvo blanco de ácido 3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]propiónico (100 mg; 0,234 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (CD_3OD) δ:1,09 (6H; d; J = 6,6 Hz); 2,09-2,22 (1H; m); 2,30-2,38 (2H; m); 2,48 (3H; s); 2,80-2,88 (2H; m); 2,90 (3H; s); 3,05 (2H; d; J = 7,5 Hz); 4,05 (2H; s); 7,26 (2H; d; J = 7,9 Hz); 7,51 (2H; d; J = 8,1 Hz).

Ejemplo 44

2-[5-(aminometil)-6-isobutil-4-(4-metilfenil)-2-propilpiridin-3-il]acetamida

1) Terc-Butil{[5-(hidroximetil)-2-isobutil-4-(4-metilfenil)-6-propilpiridin-3-il]metil}carbamato (1,40 g; rendimiento 60%) fue obtenido como polvo rosa pálido de metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)-2-propilnicotinato (2,50 g; 5,50 mmol) según un método similar al método del Ejemplo 5-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,02 (3H; d; J = 7,4 Hz); 1,38 (9H; s); 1,73-1,86 (2H; m); 2,14-2,28 (1H; m); 2,41 (3H; s); 2,76 (2H; d; J = 7,2 Hz); 2,88-2,93 (2H; m); 4,04 (2H; d; J = 5,1 Hz); 4,20 (1H; brs); 4,36 (2H; d; J = 5,8 Hz); 7,06 (2H; d; J = 7,9 Hz); 7,26 (2H; d; J = 7,35 Hz).

2) Terc-butil {[5-(cianometil)-2-isobutil-4-(4-metilfenil)-6-propilpiridin-3-il]metil}carbamato (0,82 g; rendimiento 67%) se obtuvo como un aceite de terc-butil {[5-(hidroximetil)-2-isobutil-4-(4-metilfenil)-6-propilpiridin-3-il]metil}carbamato (1,20 g; 2,81 mmol) según un método similar al método del Ejemplo 5-2).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,05 (3H; t; J = 7,4 Hz); 1,38 (9H; s); 1,78-1,90 (2H; m); 2,18-2,27 (1H; m); 2,43 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 2,81-2,86 (2H; m); 3,33 (2H; s); 4,05-4,06 (2H; m); 4,20 (1H; brs); 7,05 (2H; d; 7,9 Hz); 7,30 (2H; d; J = 7,7 Hz).

3) Terc-butil {[5-(2-amino-2-oxoetil)-2-isobutil-4-(4-metilfenil)-6-propilpiridin-3-il]metil}carbamato (814 mg, rendimiento 95%) fue obtenido como polvo blanco de terc-butil {[5-(cianometil)-2-isobutil-4-(4-metilfenil)-6-propilpiridin-3-il]metil}carbamato (0,82 g; 1,88 mmol) según un método similar al método del Ejemplo 6-1).

^{1}H-RMN (CD_3OD) δ:0,98-1,05 (9H; m); 1,38 (9H; s); 1,66-1,77 (2H; m); 2,08-2,19 (1H; m); 2,39 (3H; s); 2,76-2,80 (4H; m); 3,37 (2H; s); 3,92-3,97 (2H; m); 4,59 (1H; brs); 7,70 (2H; d; J = 8,1 Hz); 7,27 (2H; d; J = 7,7 Hz).

4) 2-[5-(Aminometil)-6-isobutil-4-(4-metilfenil)-2-propilpiridin-3-il]acetamida (31 mg, rendimiento 10%) fue obtenida como un aceite de terc-butil {[5-(2-amino-2-oxoetil)-2-isobutil-4-(4-metilfenil)-6-propilpiridin-3-il]metil}carbamato (300 mg; 0,84 mmol) según un método similar al método del Ejemplo 8-3).

^{1}H-RMN (CD_3OD) δ:0,99 (6H; d; J=6,6 Hz); 1,01 (3H; t; J=7,4 Hz); 1,63-1,71 (2H; m); 2,04-2,18 (1H; m); 2,40 (3H; s); 2,71-2,76 (2H; m); 2,79 (2H; d; J = 7,4 Hz); 3,33 (2H; s);

3,53 (2H; s); 7,11 (2H; d; J=7,9 Hz); 7,30 (2H; d; J=7,9 Hz).

Ejemplo 45

Terc-butil 5-(aminometil)-2,6-diisobutil-4-(4-metilfenil)nicotinato

1) Terc-butil 3-amino-5-metilhex-2-enoato fue obtenido como un producto en bruto (10 g) de ácido de Meldrum (14,41 g; 100 mmol) y cloruro de isovalerilo (11,5 mL; 110 mmol) según un método similar al método del Ejemplo 25-1).

2) Terc-butil 5-ciano-2,6-diisobutil-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (12,11 g, rendimiento 74%) fue obtenido como un aceite de 5-metil-3-oxohexannitrilo (5,0 g; 40 mmol), p-tolualdehído (4,8 g; 40 mmol), y el producto en bruto (9,96 g) obtenido en 1) mencionado precedentemetne, según un método similar al método del Ejemplo 1-2).

3) Terc-butil 5-ciano-2,6-diisobutil-4-(4-metilfenil)nicotinato (3,39 g; rendimiento 83%) fue obtenido de terc-butil 5-ciano-2,6-diisobutil-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (4,09 g; 10 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:0,95 (6H; d; J = 6,6 Hz); 1,00 (6H; d; J = 6,6 Hz); 1,23 (9H; s); 2,19-2,33 (1H; m); 2,41 (3H; s); 2,76 (2H; d; J = 7,5 Hz); 2,94 (2H; d; J = 7,2 Hz); 7,20-7,35 (4H; m).

4) terc-butil 5-(aminometil)-2;6-diisobutil-4-(4-metilfenil)nicotinato (2,85 g; rendimiento 86%) fue obtenido

como un aceite de terc-butil 5-ciano-2,6-diisobutil-4-(4-metilfenil)nicotinato (3,25 g; 8 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,93 (6H; d; J = 6,6 Hz); 0,97 (6H; d; J = 6,6 Hz); 1,17 (9H; s); 1,38 (2H; brs); 2,16-2,30 (2H; m); 2,39 (3H; s); 2,67 (2H; d; J = 7,5 Hz); 2,79 (2H; d; J = 7,2 Hz); 3,62 (2H; s); 7,13 (2H; d; J = 8,1 Hz); 7,21 (2H; d; J = 8,1 Hz).

Ejemplo 46

Dihidrocloruro de ácido 5-(aminometil)-2,6-diisobutil-4-(4-metilfenil)nicotínico

Dihidrocloruro de ácido 5-(aminometil)-2,6-diisobutil-4-(4-metilfenil)nicotínico (0,39 g, rendimiento 92%) fue obtenido como polvo blanco de terc-butil 5-(aminometil)-2,6-diisobutil-4-(4-metilfenil)nicotinato (0,41 g; 1 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:0,90 (6H; d; J = 6,6 Hz); 0,96 (6H; d; J = 6,6 Hz); 2,16-2,29 (2H; m); 2,37 (3H; s); 2,68 (2H; d; J = 7,2 Hz); 2,88 (2H; d; J = 7,2 Hz); 3,79 (2H; d; J = 5,1 Hz); 7,22 (2H; d; J = 8,1 Hz); 7,29 (2H; d; J = 8,1 Hz); 8,12 (3H; brs).

Ejemplo 47

P-toluensulfonato de ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]piridin-3-il}metil)amina

1) A una suspensión de p-toluensulfinato de sodio (9,0 g; 50,5 mmol) en etanol (50 mL) fue agregado bromoacetona por gotas (6,92 g; 50,5 mmol). La mezcla obtenida fue calentada bajo reflujo por 30 min., se permitió enfriar a la temperatura ambiente y fue dividida entre acetato de etilo y agua. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice para dar 1-[(4-metilfenil)sulfonil]acetona (8,0 g; rendimiento 75%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:2,41 (3H; s); 2,46 (3H; s); 4,14 (2H; s); 7,37 (2H; d; J = 8,2 Hz); 7,77 (2H; d; J = 8,2 Hz).

2) Una mezcla de 1-[(4-metilfenil)sulfonil]acetona (2,0 g; 9,4 mmol); p-tolualdehído (1,14 g; 9,4 mmol); piperidina (0,093 mL; 0,94 mmol), ácido acético (0,11 mL; 1,9 mmol) y tolueno (100 mL) fue calentada bajo reflujo usando una trampa Dean-Stark por 3 hrs. A la mezcla de reacción se le permitió enfriar a temperatura ambiente, fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida para dar 4-(4-metilfenil)-3-[(4-metilfenil)sulfonil]but-3-en-2-ona como un producto en bruto (3.5 g).

3) Una mezcla de 5-metil-3-oxohexannitrilo (14,3 g; 100 mmol), ácido acético (6,0 g; 10 mmol), acetato de amonio

(38,5 g; 500 mmol) y tolueno (200 mL) fue calentada bajo reflujo usando una trampa Dean-Stark por 17 hrs. A la mezcla de reacción se le permitió enfriar a la temperatura ambiente, fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar 3-amino-5-metilhex-2-ennitrilo como una mezcla (8m2 g). La mezcla (0,65 g) y el producto en bruto (1,7 g) obtenido en el 2) mencionado precedentemente fue disuelto en etanol (50 mL) y la mezcla fue calentada bajo reflujo por 12 hrs. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar 2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]-1,4-dihidropiridin-3-carbonitrilo (1,3 g; rendimiento 64%) como un polvo blanco.

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4) 2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]nicotinonitrilo (0,77 g, rendimiento 68%) fue obtenido como polvo blanco de 2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]-1,4-dihidropiridin-3-carbonitrilo (1,13 g, 2.7 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 2,20-2,35 (1H; m); 2,38 (3H; s); 2,39 (3H; s); 2,91 (2H; d; J = 7,2 Hz); 3,07

(3H; s); 6,86 (2H; d; J = 8,1 Hz); 7,08 (4H; d; J = 8,1 Hz); 7,23 (2H; d; J = 8,1 Hz).

Punto de fusión: 129-131°C

5) ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]piridin-3-il}metil)amina (0,64 g, rendimiento 93%) se obtuvo como un aceite incoloro de 2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]nicotinonitrilo (0,69 g; 1,6 mmol) según un método similar al método de Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,41 (2H; brs); 2,20-2,35 (1H; m); 2,38 (6H; s); 2,79 (2H; d; J = 7,2 Hz); 2,96 (3H; s); 3,40 (2H; s); 6,76 (2H; d; J = 8,1 Hz); 7,03 (2H; d; J = 8,3 Hz); 7,09 (2H; d; J = 8,1 Hz); 7,27 (2H; d; J = 8,3 Hz).

6) A una solución de ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]piridin-3-il}metil)amina (0,64 g, 1,5 mmol) en etanol (5 mL) fue agregado el por gotas una solución de monohidrato de ácido p-toluensulfónico (0,29 g, 1,5 mmol) en etanol (5 mL) a la temperatura ambiente. Los cristales precipitados fueron recolectados por filtración, se lavaron con etanol frio y se secaron para dar p-toluensulfonato de ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]piridin-3-il}metil)amina (0,57 g; rendimiento 63%) como un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ:0,94 (6H; d; J = 6,6 Hz); 2,15-2,30 (1H;

m); 2,29 (3H; s); 2,37 (6H; s); 2,78 (2H; d; J = 7,0 Hz); 2,84 (3H; s); 3,57 (2H; s); 6,87 (2H; d; J = 7,9 Hz); 7,11 (4H; d; J = 8,5 Hz); 7,25-7,30 (4H; m); 7,47 (2H; d; J = 7,9 Hz); 7,76 (3H; brs).

Punto de fusión: 234-235°C

Ejemplo 48

Terc-butil 5-(aminometil)-2-bencil-6-isobutil-4-(4-metilfenil)nicotinato

1) terc-butil 3-amino-4-fenilbut-2-enoato fue obtenido como un producto en bruto (16 g) de ácido de Meldrum (14,41 g, 100 mmol) y cloruro de fenilacetilo (14,5 mL, 110 mmol) según un método similar al método del Ejemplo 25-1).

2) Terc-butil 2-bencil-5-ciano-6-isobutil-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (14,1 g; rendimiento 79%) se obtuvo como un aceite de 5-metil-3-oxohexannitrilo (5,0 g; 40 mmol), p-tolualdehído (4,8 g; 40 mmol), y el producto en bruto (16 g) que se obtuvo en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 1-2).

3) Terc-butil 2-bencil-5-ciano-6-isobutil-4-(4-metilfenil)nicotinato (2,92 g; rendimiento 66%) fue obtenido de terc-butil 2-bencil-5-ciano-6-isobutil-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (4,43 g, 10 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,10 (9H; s); 2,19-

2,35 (1H; m); 2,40 (3H; s); 2,94 (2H; d; J = 7,2 Hz); 4,28 (2H; s); 7,16-7,32 (9H; m).

4) Terc-butil 5-(aminometil)-2-bencil-6-isobutil-4-(4-metilfenil)nicotinato (2.45 g, rendimiento 55%) se obtuvo como un aceite del terc-butilo 2-bencil-5-ciano-6-isobutil-4-(4-metilfenil)nicotinato (4,40 g, 10 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,95 (6H; d; J = 6,6 Hz); 1,05 (9H; s); 1,26 (2H; brs); 2,21-2,30 (1H; m); 2,38 (3H; s); 2,79 (2H; d; J = 7,5 Hz); 3,62 (2H; s); 4,20 (2H; s); 7,11-7,31 (9H; m).

Ejemplo 49

Dihidrocloruro de ácido 5-(aminometil)-2-bencil-6-isobutil-4-(4-metilfenil)nicotínico

Dihidrocloruro de ácido 5-(Aminometil)-2-bencil-6-isobutil-4-(4-metilfenil)nicotínico (0.38 g, rendimiento 82%) fue obtenido como polvo blanco de terc-butil 5-(aminometil)-2-bencil-6-isobutil-4-(4-metilfenil)nicotinato (0,44 g; 1 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:0,93 (6H; d; J = 6,3 Hz); 2,16-2,29 (1H; m); 2,37 (3H; s); 2,82 (2H; d; J = 6,6 Hz); 3,77 (2H; d; J = 4,8 Hz); 4,13 (2H; s); 7,15-7,31 (9H; m); 8,16 (3H; brs).

Ejemplo 50

Dihidrocloruro de ácido 5-(aminometil)-6-isobutil-4-(4-metilfenil)-2-fenilnicotínico

1) Etil 3-amino-3-fenilacrilatose obtenido como un producto en bruto (9.5 g) de etil 3-oxo-3-fenilpropanoato (9,61 g; 50 mmol) y acetato de amonio (19,27 g; 250 mmol) según un método similar al método del Ejemplo 12-1).

2) Etil 5-ciano-6-isobutil-4-(4-metilfenil)-2-fenil-1,4-dihidropiridin-3-carboxilato (9,52 g; rendimiento 59%) fue obtenido como un aceite de 5-metil-3-oxohexannitrilo (5,0 g; 40 mmol), p-tolualdehído (4,8 g; 40 mmol) y el producto en bruto (9,5 g) obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 1-2).

3) Etil 5-ciano-6-isobutil-4-(4-metilfenil)-2-fenilnicotinato (4,11 g; rendimiento 85%) fue obtenido como un aceite de etil 5-ciano-6-isobutil-4-(4-metilfenil)-2-fenil-1,4-dihidropiridin-3-carboxilato (4,81 g; 12 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:0,85 (3H; t; J = 7,2 Hz); 1,05 (6H; d; J = 6,6 Hz); 2,29-2,44 (4H; m); 3,05 (2H; d; J = 7,2 Hz); 3,91 (2H; q; J = 7,2 Hz); 7,26-7,33 (4H; m); 7,43-7,48 (3H; m); 7,624-7,69 (2H; m).

4) Etil 5-(aminometil)-6-isobutil-4-(4-metilfenil)-2-fenilnicotinato (3,63 g; rendimiento 90%) fue obtenido como un aceite de etil 5-ciano-6-isobutil-4-(4-metilfenil)-2-fenilnicotinato (4,40 g; 10 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ: 0,80 (3H; t; J = 7,2 Hz); 1,03 (6H; d; J =

6,6 Hz); 1,36 (2H; bes); 2,29-2,42 (4H; m); 2,90 (2H; d; J = 7,2 Hz); 3,70 (2H; s); 3,81 (2H; q; J = 7,2 Hz); 7,17 (2H; d; J = 8,1 Hz); 7,23 (2H; d; J = 8,1 Hz); 7,35-7,43 (3H; m); 7,62-7,65 (2H; m).

5) Una mezcla de etil 5-(aminometil)-6-isobutil-4-(4-metilfenil)-2-fenilnicotinato (0,80 g; 2 mmol), 6N ácido clorhídrico (20 mL) y ácido acético (10 mL) fueron calentados bajo reflujo durante 3 días. La mezcla de reacción fue concentrada bajo presión reducida. Fue agregado tetrahidrofurano (20 mL) y 1N solución de hidróxido de sodio acuosa (30 mL) al residuo. A la mezcla obtenida fue agregado dicarbonato de di-terc-butilo (0,55 mL; 2,4 mmol) y la mezcla resultante fue agitada a temperatura ambiente por 2 hrs. La mezcla de reacción fue acidificada con 1N ácido clorhídrico y fue extraída con acetato de etilo. El extracto fue lavado con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de silicagel para dar ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)-2-fenilnicotínico (0.38 g, 0.8 mmol) como un aceite. Entonces, dihidrocloruro de ácido 5-(Aminometil)-6-isobutil-4-(4-metilfenil)-2-fenilnicotínico (0,31 g; rendimiento 88%) fue obtenido como polvo blanco de aceite según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,01 (6H; d; J = 6,6 Hz); 2,24-2,35 (1H; m); 2,38 (3H; s); 2,93 (2H; d; J = 6,9 Hz); 3,82 (2H; d; J = 5,1 Hz); 7,26-7,32 (4H; m); 7,44-7,52 (3H; m); 7,66-7,69 (2H; m); 8,38 (3H; brs).

Ejemplo 51

Metil 5-(aminometil)-2-etil-6-isobutil-4-(4-metilfenil)nicotinato

1) Metil 3-aminopent-2-enoato fue obtenido como un producto en bruto (6,4 g) de metil 3-oxopentaneoato (6,50 g, 50 mmol) y acetato de amonio (19,27 g; 250 mmol) según un método similar al método del Ejemplo 12-1).

2) Metil 5-ciano-2-etil-6-isobutil-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (4,12 g; rendimiento 48%) fue obtenido como un aceite de 5-metil-3-oxohexannitrilo (5,0 g; 40 mmol), p-tolualdehído (4,8 g; 40 mmol) y el producto en bruto (3,2 g) obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 1-2).

3) Metil 5-ciano-2-etil-6-isobutil-4-(4-metilfenil)nicotinato (3,41 g, rendimiento 84%) fue obtenido de metil 5-ciano-2-etil-6-isobutil-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (4,06 g; 12 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,6 Hz); 1,32 (3H; t; J = 7,5 Hz); 2,24-2,36 (1H; m); 2,41 (3H; s); 2,85 (2H; q; J =

7,5 Hz); 2,96 (2H; d; J = 6,9 Hz); 3,59 (3H; s); 7,24-7,30 (4H; m).

4) Metil 5-(aminometil)-2-etil-6-isobutil-4-(4-metilfenil)nicotinato (2,49 g; rendimiento 73%) fue obtenido como polvo blanco de metil 5-ciano-2-etil-6-isobutil-4-(4-metilfenil)nicotinato (4,40 g, 10 mmol) según un método similar al método de Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,29 (3H; t; J = 7,5 Hz); 2,18-2,31 (1H; m); 2,34 (3H; s); 2,77 (2H; q; J = 7,5 Hz); 2,81 (2H; d; J = 7,2 Hz); 3,49 (3H; s); 3,65 (2H; s); 7,11 (2H; d; J = 8,0 Hz); 7,21 (2H; d; J = 8,0 Hz).

Ejemplo 52

Dihidrocloruro de ácido 5-(aminometil)-2-etil-6-isobutil-4-(4-metilfenil)nicotínico

Dihidrocloruro de ácido 5-(Aminometil)-2-etil-6-isobutil-4-(4-metilfenil)nicotínico (0,30 g; rendimiento 82%) fue obtenido como polvo blanco de metil 5-(aminometil)-2-etil-6-isobutil-4-(4-metilfenil)nicotinato (0,34 g; 1 mmol) según un método similar al método del Ejemplo 50-5).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 1,26 (3H; t; J = 7,5 Hz); 2,17-2,26 (1H; m); 2,37 (3H; s); 2,89 (2H; q; J = 7,3 Hz); 3,00 (2H; d; J = 6,9 Hz); 3,81 (2H; d; J = 6,0 Hz); 7,25 (2H; d; J = 8,2 Hz); 7,30 (2H; d; J = 8,2 Hz); 8,38 (3H; brs).

Ejemplo 53

Maleato de ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico

A una solución mezcla de ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (114 mg; 0,350 mmol), acetonitrilo (2 mL) y agua (2 mL) fue agregada el ácido maléico (40,6 mg; 0,350 mmol) y la mezcla fue agitada a la temperatura ambiente. Después de la disolución del ácido maléico, fue agregado acetonitrilo (8 mL), y la mezcla fue agitada a la temperatura ambiente por 1 hr. La solución obtenida fue concentrada bajo presión reducida, y acetonitrilo (10 mL) fue agregado al residuo. La mezcla fue agitada a la temperatura ambiente por 1 hr. Los cristales precipitados fueron recolectados por filtración para dar maleato de ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (92,6 mg; 60%) como cristales en polvo incoloros.

^{1}H-RMN (DMSO-d_6) δ:1,00 (9H; s); 2,36 (3H; s); 2,49 (3H; s); 2,81 (2H; s); 3,84 (2H; s); 6,01 (2H; s); 7,17-7,21 (2H; m); 7,27-7,31 (2H; m).

Ejemplo 54

Tartarato de ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico

A una solución mezcla de ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (114 mg; 0,350 mmol),

acetonitrilo (2 mL) y agua (2 mL) fue agregado ácido tartárico (40,6 mg; 0,350 mmol), y la mezcla fue agitada a la temperatura ambiente. Después de la disolución del ácido tartárico, fue agregado acetonitrilo (8 mL), y la mezcla fue agitada a la temperatura ambiente por 1 hr. La solución obtenida fue concentrada bajo presión reducida, y fue agregado acetonitrilo (10 mL) al residuo. La mezcla fue agitada a la temperatura ambiente por 1 hr. Los cristales precipitados fueron recolectados por filtración para dar tartarato de ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (129 mg, 77%) como cristales en polvo incoloros.

^{1}H-RMN (DMSO-d_6) δ:0,98 (9H; s); 2,35 (3H; s); 2,44 (3H; s); 2,79 (2H; s); 3,75 (2H; s); 3,96 (2H; s); 7,15-7,19 (2H; m); 7,21-7,25 (2H; m).

Ejemplo 55

Terc-butil 5-(aminometil)-2-isobutil-4-(4-metilfenil)-6-neopentilnicotinato

1) Terc-butil 3-amino-5-metilhex-2-enoato fue obtenido como un producto en bruto (10 g) del ácido de Meldrum (14,41 g; 100 mmol) y cloruro de isovalerilo (11,5 mL; 110 mmol) según un método similar al método del Ejemplo 25-1).

2) Terc-butil 5-ciano-2-isobutil-4-(4-metilfenil)-6-neopentil-1,4-dihidropiridin-3-carboxilato (3,75 g; rendimiento 22%) fue obtenido como un aceite de 5,5-dimetil-

3-oxohexannitrilo (5,57 g; 40 mmol), p-tolualdehido (4,81 g; 40 mmol) y el producto en bruto (10 g) obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 1-2).

3) Terc-butil 5-ciano-2-isobutil-4-(4-metilfenil)-6-neopentilnicotinato (1,66 g, rendimiento 49%) fue obtenido del terc-butil 5-ciano-2-isobutil-4-(4-metilfenil)-6-neopentil-1,4-dihidropiridin-3-carboxilato (3,38 g; 10 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:0,95 (6H; d; J = 6,6 Hz); 1,06 (9H; s); 1,24 (9H; s); 2,22-2,35 (1H; m); 2,40 (3H; s); 2,76 (2H; d; J = 7,2 Hz); 3,00 (2H; s); 7,19-7,35 (4H; m).

4) Terc-butil 5-(aminometil)-2-isobutil-4-(4-metilfenil)-6-neopentilnicotinato (1,34 g; rendimiento 89%) fue obtenido como cristales blancos de terc-butil 5-ciano-2-isobutil-4-(4-metilfenil)-6-neopentilnicotinato (3,25 g, 8 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,93 (6H; d; J = 6,6 Hz); 1,02 (9H; s); 1,17 (9H; s); 1,24 (2H; brs); 2,22-2,31 (1H; m); 2,39 (3H; s); 2,66 (2H; d; J = 7,5 Hz); 2,87 (2H; s); 3,68 (2H; s); 7,13 (2H; d; J = 8,0 Hz); 7,21 (2H; d; J = 8,0 Hz).

Ejemplo 56

Terc-butil 5-(aminometil)-2-bencil-4-(4-metilfenil)-6-neopentilnicotinato

1) Terc-butil 3-amino-4-fenilbut-2-enoato fue obtenido como un producto en bruto (16 g) del ácido de Meldrum (14,41 g; 100 mmol) y cloruro de fenilacetilo (14,5 mL, 110 mmol)' según un método similar al método del Ejemplo 25-1).

2) Terc-butil 2-bencil-5-ciano-4-(4-metilfenil)-6-neopentil-1,4-dihidropiridin-3-carboxilato (12,5 g; rendimiento 68%) fue obtenido como un aceite de 5,5-dimetil-3-oxohexannitrilo (5,57 g, 40 mmol), p-tolualdehído (4,81 g; 40 mmol), y el producto en bruto (11,6 g) obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 1-2).

3) Terc-butil 2-bencil-5-ciano-4-(4-metilfenil)-6-neopentilnicotinato (6,8 g; rendimiento 100%) fue obtenido del terc-butil 2-bencil-5-ciano-4-(4-metilfenil)-6-neopentil-1,4-dihidropiridin-3-carboxilato (6,8 g; 10 mmol) según un método similar al método del Ejemplo 23-3).

4) Terc-butil 5-(aminometil)-2-bencil-4-(4-metilfenil)-6-neopentilnicotinato (0,48 g, rendimiento 15%) fue obtenido como cristales blancos de terc-butil 2-bencil-5-ciano-4-(4-metilfenil)-6-neopentilnicotinato (3.18 g, 7 mmol) según un método similar al método de Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,96 (9H; s); 1,07 (9H; s); 2,39 (3H; s); 2,85 (2H; s); 3,67 (2H; s); 4,18 (2H; s); 7,11-7,32 (9H; m).

Ejemplo 57

Terc-butil 5-(aminometil)-2-etil-4-(4-metilfenil)-6-

neopentilnicotinato

1) Terc-butil 3-aminopent-2-enoato fue obtenido como un producto en bruto (8,5 g) del ácido de Meldrum (14,41 g, 100 mmol) y cloruro de propionilo (9,6 mL, 110 mmol) según un método similar al método del Ejemplo 25-1).

2) Terc-butil 5-ciano-2-etil-4-(4-metilfenil)-6-neopentil-1,4-dihidropiridin-3-carboxilato (6,0 g; rendimiento 38%) fue obtenido como un aceite de 5,5-dimetil-3-oxohexannitrilo (5,57 g, 40 mmol), p-tolualdehído (4,81 g; 40 mmol) y el producto en bruto (8,5 g) obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 1-2).

3) Terc-butil 5-ciano-2-etil-4-(4-metilfenil)-6-neopentilnicotinato (2,58 g, rendimiento 43%) fue obtenido como un sólido amarillo pálido del terc-butil 5-ciano-2-etil-4-(4-metilfenil)-6-neopentil-1,4-dihidropiridin-3-carboxilato (5,92 g; 15 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,07 (9H; s); 1,26 (9H; s); 1,34 (3H; t; J = 7,5 Hz); 2,41 (3H; s); 2,89 (2H; q; J = 7,5 Hz); 3,01 (2H; s); 7,20-7,29 (4H; m).

4) Terc-butil 5-(aminometil)-2-etil-4-(4-metilfenil)-6-neopentilnicotinato (1,56 g; rendimiento 65%) fue obtenido como un aceite del terc-butil 5-ciano-2-etil-4-(4-metilfenil)-6-neopentilnicotinato (2,36 g; 6 mmol) según un

método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:1,03 (9H; s); 1,19 (9H; s); 1,28 (2H; brs); 1,32 (3H; t; J = 7,5 Hz); 2,39 (3H; s); 2,80 (2H; q; J = 7,5 Hz); 2,87 (2H; s); 3,68 (2H; s); 7,13 (2H; d; J = 8,1 Hz); 7,21 (2H; d; J = 8,1 Hz).

Ejemplo 58

Dihidrocloruro de ácido 5-(aminometil)-2-etil-4-(4-metilfenil)-6-neopentilnicotínico

Dihidrocloruro de ácido 5-(aminometil)-2-etil-4-(4-metilfenil)-6-neopentilnicotínico (0,37 g; rendimiento 90%) fue obtenido como polvo blanco del terc-butil 5-(aminometil)-2-etil-4-(4-metilfenil)-6-neopentilnicotinato (0,39 g, 1 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:1,02 (9H; s); 1,26 (3H; t; J = 7,5 Hz); 2,37 (3H; s); 2,78 (2H; q; J = 7,5 Hz); 2,92 (2H; s); 3,83 (2H; d; J = 5,4 Hz); 7,21 (2H; d; J = 8,0 Hz); 7,29 (2H; d; J = 8,0 Hz); 8,13 (3H; brs).

Ejemplo 59

Terc-butil 5-(aminometil)-4-(4-metilfenil)-6-neopentil-2-propilnicotinato

1) Terc-butil 3-aminohex-2-enoato fue obtenido como un producto en bruto (9,2 g) del ácido de Meldrum (14,41 g; 100 mmol) y cloruro de butirilo (11,4 mL, 110 mmol) según un método similar al método del Ejemplo 25-1).

2) Terc-butil 5-ciano-4-(4-metilfenil)-6-neopentil-2-propil-1,4-dihidropiridin-3-carboxilato (10,1 g; rendimiento 61%) fue obtenido como un aceite de 5,5-dimetil-3-oxohexannitrilo (5,57 g, 40 mmol), p-tolualdehído (4,81 g; 40 mmol) y el producto en bruto (16 g) obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 1-2).

3) Terc-butil 5-ciano-4-(4-metilfenil)-6-neopentil-2-propilnicotinato (5,74 g, rendimiento 58%) fue obtenido como un aceite de terc-butil 5-ciano-4-(4-metilfenil)-6-neopentil-2-propil-1,4-dihidropiridin-3-carboxilato (9,8 g; 24 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,00 (3H; t; J = 7,5 Hz); 1,06 (9H; s); 1,26 (9H; s); 1,75-1,88 (2H; m); 2,41 (3H; s); 2,81-2,86 (2H; m); 3,00 (2H; s); 7,18-7,30 (4H; m).

4) terc-butil 5-(aminometil)-4-(4-metilfenil)-6-neopentil-2-propilnicotinato (3,36 g, rendimiento 74%) fue obtenido como cristales blancos de terc-butil 5-ciano-4-(4-metilfenil)-6-neopentil-2-propilnicotinato (4,47 g; 11 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,98 (3H; t; J = 7,3 Hz); 1,02 (9H; s); 1,14 (2H; brs); 1,14 (9H; s); 1,73-1,86 (2H; m); 2,39 (3H; s); 2,72-2,77 (2H; m); 2,87 (2H; s); 3,68 (2H; s); 7,13 (2H; d; J = 8,1 Hz); 7,21 (2H; d; J = 8,1 Hz).

Ejemplo 60

Dihidrocloruro de ácido 5-(aminometil)-4-(4-metilfenil)-6-neopentil-2-propilnicotínico

Dihidrocloruro de ácido 5-(aminometil)-4-(4-metilfenil)-6-neopentil-2-propilnicotínico (0,38 g; rendimiento 90%) fue obtenido como polvo blanco de terc-butil 5-(aminometil)-4-(4-metilfenil)-6-neopentil-2-propilnicotinato (0,41 g; 1 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:0,93 (3H; t; J = 7,3 Hz); 1,02 (9H; s); 1,69-1,81 (2H; m); 2,37 (3H; s); 2,74-2,79 (2H; m); 2,94 (2H; brs); 3,84 (2H; d; J = 5,1 Hz); 7,22 (2H; d; J = 8,0 Hz); 7,29 (2H; d; J = 8,0 Hz); 8,14 (3H; brs).

Ejemplo 61

Terc-butil 5-(aminometil)-2-isopropil-4-(4-metilfenil)-6-neopentilnicotinato

1) Terc-butil 3-amino-4-metilpent-2-enoato fue obtenido como un producto en bruto (9,2 g) del ácido de Meldrum (14,41 g; 100 mmol) y cloruro de isobutirilo (11,4 mL; 110 mmol) según un método similar al método del Ejemplo 25-1).

2) terc-butil 5-ciano-2-isopropil-4-(4-metilfenil)-6-neopentil-1,4-dihidropiridin-3-carboxilato (4,91 g; rendimiento 30%) fue obtenido como un aceite de 5,5-dimetil-3-oxohexannitrilo (5,57 g; 40 mmol), p-tolualdehído (4,81 g, 40 mmol) y el producto en bruto (9,2 g) obtenido en el 1) mencionado precedentemente, según un método similar al método

del Ejemplo 1-2).

3) terc-butil 5-ciano-2-isopropil-4-(4-metilfenil)-6-neopentilnicotinato (2,48 g; rendimiento 50%) fue obtenido de terc-butil 5-ciano-2-isopropil-4-(4-metilfenil)-6-neopentil-1,4-dihidropiridin-3-carboxilato (4,90 g; 12 mmol) según un método similar al método del Ejemplo 23-3).

4) terc-butil 5-(aminometil)-2-isopropil-4-(4-metilfenil)-6-neopentilnicotinato (1,26 g; rendimiento 51%) fue obtenido como cristales blancos de terc-butil 5-ciano-2-isopropil-4-(4-metilfenil)-6-neopentilnicotinato (3,25 g; 8 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:1,04 (9H; s); 1,18 (9H; s); 1,30 (6H; d; J = 6,9 Hz); 1,32 (2H; brs); 2,39 (3H; s); 2,85 (2H; s); 3,04-3,13 (1H; m); 3,66 (2H; s); 7,13 (2H; d; J = 8,0 Hz); 7,20 (2H; d; J = 8,0 Hz).

Ejemplo 62

Dihidrocloruro de ácido 5-(aminometil)-2-isopropil-4-(4-metilfenil)-6-neopentilnicotínico

Dihidrocloruro de ácido 5-(Aminometil)-2-isopropil-4-(4-metilfenil)-6-neopentilnicotínico (0,37 g; rendimiento 88%) fue obtenido como polvo blanco de terc-butil 5-(aminometil)-2-isopropil-4-(4-metilfenil)-6-neopentilnicotinato (0,42 g; 1 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:1,04 (9H; s); 1,25 (6H; d; J = 6,6 Hz);

2,36 (3H; s); 2,90 (2H; s); 3,03-3,13 (1H; m); 3,81 (2H; d; J = 5,4 Hz); 7,22 (2H; d; J = 8,2 Hz); 7,28 (2H; d; J = 8,2 Hz); 8,18 (3H; brs).

Ejemplo 63

Dihidrocloruro de ácido 5-(aminometil)-2-isobutil-4-(4-metilfenil)-6-neopentilnicotínico

Dihidrocloruro de ácido 5-(Aminometil)-2-isobutil-4-(4-metilfenil)-6-neopentilnicotínico (0,41 g, rendimiento 93%) fue obtenido como polvo blanco del terc-butil 5-(aminometil)-2-isobutil-4-(4-metilfenil)-6-neopentilnicotinato (0,42 g, 1 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:0,89 (6H; d; J = 6,6 Hz); 1,02 (9H; s); 2,18-2,31 (1H; m); 2,37 (3H; s); 2,66 (2H; d; J = 7,2 Hz); 2,91 (2H; s); 3,84 (2H; d;J = 5,1 Hz); 7,21 (2H; d; J = 8,1 Hz); 7,29 (2H; d; J = 8,1 Hz); 8,08 (3H; brs).

Ejemplo 64

Dihidrocloruro de ácido 5-(aminometil)-2-bencil-4-(4-metilfenil)-6-neopentilnicotínico

Dihidrocloruro de ácido 5-(Aminometil)-2-bencil-4-(4-metilfenil)-6-neopentilnicotínico (0,43 g; rendimiento 91%) fue obtenido como polvo blanco del terc-butil 5-(aminometil)-2-bencil-4-(4-metilfenil)-6-neopentilnicotinato (0,45 g; 1 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:0,95 (9H; s); 2,37 (3H; s); 2,89 (2H; s);

3,82 (2H; d; J = 5,4 Hz); 4,14 (2H; s); 7,18-7,31 (9H; m); 8,17 (3H; brs).

Ejemplo 65

dihidrocloruro de metil 5-(aminometil)-6-butilo-2-metil-4-(4-metilfenil)nicotinato

1) Metil 6-butil-5-ciano-2-metil-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (39 g, rendimiento 24%) fue obtenido como cristales de 3-oxoheptannitrilo (64 g, 500 mmol) según un método similar al método del Ejemplo 1-2).

^{1}H-RMN ($CDCl_3$) δ:0,92 (3H; t; J = 7,3 Hz); 1,30-1,42 (2H; m); 1,49-1,60 (2H; m); 2,30 (3H; s); 2,34-2,39 (2H; m); 2,35 (3H; s); 3,58 (3H; s); 4,56 (1H; s); 5,77 (1H; s); 7,07-7,14 (4H; m).

2) Metil 6-butil-5-ciano-2-metil-4-(4-metilfenil)nicotinato (25 g, rendimiento 65%) fue obtenido como cristales de metil 6-butil-5-ciano-2-metil-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (25 g, 77 mmol) según un método similar al método del Ejemplo 1-3).

^{1}H-RMN ($CDCl_3$) δ:0,97 (3H; t; J = 7,3 Hz); 1,40-1,52 (2H; m); 1,74-1,84(2H; m); 2,41 (3H; s); 2,62 (3H; s); 3,04-3,09 (2H; m); 3,60 (3H; s); 7,23-7,29 (4H; m).

3) Metil 5-(aminometil)-6-butil-2-metil-4-(4-metilfenil)nicotinato (17 g, rendimiento 68%) fue obtenido como un aceite de metil 6-butil-5-ciano-2-metil-4-(4-

metilfenil)nicotinato (4 g; 11,9 mmol) según un método similar al método del Ejemplo 1-4). El aceite (3 g) fue disuelto en acetato de etilo (10 mL) y fue agregado 4N solución ácido clorhídrico acetato de etilo (10 mL). La mezcla fue concentrada bajo presión reducida para dar dihidrocloruro de metil 5-(aminometil)-6-butil-2-metil-4-(4-metilfenil)nicotinato como un polvo.

^{1}H-RMN (DMSO-d_6) δ:0,95 (3H; t; J = 7,3 Hz); 1,38-1,51 (2H; m); 1,65-1,75 (2H; m); 2,37 (3H; s); 2,53 (3H; s); 2,98-3,03 (2H; m); 3,47 (3H; s); 3,82 (2H; d; J = 5,5 Hz); 7,19 (2H; d; J = 8,1 Hz); 7,30 (2H; d; J = 8,1 Hz); 8,38 (3H; s).

Ejemplo 66

Dihidrocloruro de ácido 5-(aminometil)-6-butil-2-metil-4-(4-metilfenil)nicotínico

1) Metil 5-{[(terc-butoxicarbonil)amino]metil}-6-butil-2-metil-4-(4-metilfenil)nicotinato (16,3 g; rendimiento 89%) fue obtenido como cristales de metil 5-(aminometil)-6-butil-2-metil-4-(4-metilfenil)nicotinato (14 g; 42,9 mmol) según un método similar al método del Ejemplo 2-1).

2) Ácido 5-{[(terc-Butoxicarbonil)amino]metil}-6-butil-2-metil-4-(4-metilfenil)nicotínico (1,5 g; rendimiento 77%) fue obtenido como cristales de metil 5-{[(terc-butoxicarbonil)amino]metil}-6-butil-2-metil-4-(4-metilfenil)nicotinato (2,0 g; 4,7 mmol) según un método similar al método del Ejemplo 2-2).

3) Dihidrocloruro de ácido 5-(Aminometil)-6-butil-2-metil-4-(4-metilfenil)nicotínico (0,56 g; rendimiento 86%) fue obtenido como polvo blanco de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-butil-2-metil-4-(4-metilfenil)nicotínico (0,7 g; 1,7 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,95 (3H; t; J = 7,4 Hz); 1,39-1,49 (2H; m); 1,65-1,75 (2H; m); 2,37 (3H; s); 2,61 (3H; s); 3,03-3,08 (2H; m); 3,81 (2H; d; J = 5,3 Hz); 7,24 (2H; d; J = 8,1 Hz); 7,31 (2H; d; J = 8,1 Hz); 8,40 (3H; s).

Ejemplo 67

Dihidrocloruro de metil 5-(aminometil)-2-metil-4-(4-metilfenil)-6-propilnicotinato

1) Metil 5-ciano-2-metil-4-(4-metilfenil)-6-propil-1,4-dihidropiridin-3-carboxilato (60 g, rendimiento 39%) fue obtenido como un aceite de 3-oxohexannitrilo (60 g, 500 mmol) según un método similar al método del Ejemplo 1-2).

^{1}H-RMN ($CDCl_3$) δ:0,96 (3H; t; J = 7,4 Hz); 1,54-1,66 (2H; m); 2,30 (3H; s); 2,32-2,41 (2H; m); 2,35 (3H; s); 3,58 (3H; s); 4,56 (1H; s); 5,80 (1H; s); 7,09 (2H; d; J = 8,1 Hz); 7,13 (2H; d; J = 8,1 Hz).

2) Metil 5-ciano-2-metil-4-(4-metilfenil)-6-propilnicotinato (34,8 g; rendimiento 58%) fue obtenido como cristales de metil 5-ciano-2-metil-4-(4-metilfenil)-6-propil-

1,4-dihidropiridin-3-carboxilato (60 g, 193 mmol) según un método similar al método del Ejemplo 1-3).

^{1}H-RMN ($CDCl_3$) δ:1,05 (3H; t; J = 7,4 Hz); 1,79-1,91 (2H; m); 2,41 (3H; s); 2,62 (3H; s); 3,02-3,07 (2H; m); 3,60 (3H; s); 7,23-7,29 (4H; m).

3) Metil 5-(aminometil)-2-metil-4-(4-metilfenil)-6-propilnicotinato (15 g, rendimiento 67%) fue obtenido como un aceite de metil 5-ciano-2-metil-4-(4-metilfenil)-6-propilnicotinato (22 g; 71,3 mmol) según un método similar al método de Ejemplo 1-4). El aceite (2 g) fue disuelto en acetato de etilo (10 mL) y fue agregado 4N solución ácido clorhídrico acetato de etilo (10 mL). La mezcla fue concentrada bajo presión reducida para dar dihidrocloruro de metil 5-(aminometil)-2-metil-4-(4-metilfenil)-6-propilnicotinato como un polvo.

^{1}H-RMN (DMSO-d_6) δ:1,02 (3H; t; J = 7,4 Hz); 1,69-1,82 (2H; m); 2,37 (3H; s); 2,53 (3H; s); 2,96-3,02 (2H; m); 3,47 (3H; s); 3,82 (2H; d; J = 5,5 Hz); 7,19 (2H; d; J = 8,1 Hz); 7,31 (2H; d; J = 8,1 Hz); 8,38 (3H; s).

Ejemplo 68

Dihidrocloruro de ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-propilnicotínico

1) Metil 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-propilnicotinato (12 g, rendimiento 70%) fue

obtenido como cristales de metil 5-(aminometil)-2-metil-4-(4-metilfenil)-6-propilnicotinato (13 g; 41,6 mmol) según un método similar al método del Ejemplo 2-1).

^{1}H-RMN ($CDCl_3$) δ:1,03 (3H; t; J = 7,4 Hz); 1,39 (9H; s); 1,72-1,79 (2H; m); 2,38 (3H; s); 2,53 (3H; s); 2,84-2,90 (2H; m); 3,49 (3H; s); 4,15 (2H; d; J = 5,1 Hz); 4,25 (1H; s); 7,05 (2H; d; J = 8,1 Hz); 7,20 (2H; d; J = 8,1 Hz).

2) El ácido 5-{[(terc-Butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-propilnicotínico (1,6 g; rendimiento 83%) fue obtenido como cristales de metil 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-propilnicotinato (2 g; 4,8 mmol) según un método similar al método del Ejemplo 2-2).

^{1}H-RMN (DMSO-d_6) δ:0,96 (3H; t; J = 7,4 Hz); 1,35 (9H; s); 1,64-1,76 (2H; m); 2,33 (3H; s); 2,44 (3H; s) 2,67-2,72 (2H; m); 3,87 (2H; d; J = 4,5 Hz); 6,99 (1H; s); 7,16-7,22 (4H; m); 12,92 (1H; s).

3) Dihidrocloruro de ácido 5-(Aminometil)-2-metil-4-(4-metilfenil)-6-propilnicotínico (0,75 g; rendimiento 96%) fue obtenido como polvo blanco de ácido 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-propilnicotínico (0,7 g; 2,1 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,02 (3H; t; J = 7,4 Hz); 1,69-1,82 (2H;

m); 2,37 (3H; s); 2,62 (3H; s); 3,01-3,07 (2H; m); 3,82 (2H; d; J = 5,3 Hz); 7,24 (2H; d; J = 8,1 Hz); 7,31 (2H; d; J = 8,1 Hz); 8,41 (3H; s).

Ejemplo 69

Dihidrocloruro de ácido 5-(aminometil)-4-(4-fluorofenil)-6-isobutil-2-metilnicotínico

1) Metil 5-{[(terc-butoxicarbonil)amino]metil}-4-(4-fluorofenil)-6-isobutil-2-metilnicotinato (2,60 g; rendimiento 99%) fue obtenido como un sólido blanco de metil 5-(aminometil)-4-(4-fluorofenil)-6-isobutil-2-metilnicotinato (2,00 g; 6,05 mmol) según un método similar al método del Ejemplo 2-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,16-2,26 (1H; m); 2,54 (3H; s); 2,78 (2H; d; J = 7,2 Hz); 3,51 (3H; s); 4,08-4,17 (2H; m); 4,22 (1H; brs); 7,07-7,20 (4H; m).

2) El ácido 5-{[(terc-Butoxicarbonil)amino]metil}-4-(4-fluorofenil)-6-isobutil-2-metilnicotínico (2,01 g; rendimiento 79%) fue obtenido como un sólido amarillo de metil 5-{[(terc-butoxicarbonil)amino]metil}-4-(4-fluorofenil)-6-isobutil-2-metilnicotinato (2,60 g; 6,24 mmol) según un método similar al método del Ejemplo 2-2).

^{1}H-RMN (CD_3OD) δ:1,04 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,12-2,22 (1H; m); 2,71 (3H; s); 2,94 (2H; d; J = 7,4 Hz); 4,13

(2H; s); 7,17-7,25 (2H; m); 7,32-7,39 (2H; m).

3) Dihidrocloruro de ácido 5-(Aminometil)-4-(4-fluorofenil)-6-isobutil-2-metilnicotínico (0,20 g; rendimiento 76%) fue obtenido como un sólido blanco de ácido 5-{[(terc-butoxicarbonil)amino]metil}-4-(4-fluorofenil)-6-isobutil-2-metilnicotínico (0,28 g; 0,673 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (CD_3OD) δ:1,04-1,13 (6H; m); 2,13-2,28 (1H; m); 2,78-2,86 (3H; m); 3,02-3,11 (2H; m); 4,13-4,20 (2H; m); 7,30-7,38 (2H; m); 7,42-7,51 (2H; m).

Ejemplo 70

Dihidrocloruro de ácido 5-(aminometil)-4-(2,6-difluorofenil)-6-isobutil-2-metilnicotínico

1) Metil 5-{[(terc-butoxicarbonil)amino]metil}-4-(2,6-difluorofenil)-6-isobutil-2-metilnicotinato (2,49 g; rendimiento 87%) fue obtenido como un sólido blanco de metil 5-(aminometil)-4-(2,6-difluorofenil)-6-isobutil-2-metilnicotinato (2,00 g; 6,38 mmol) según un método similar al método del Ejemplo 2-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,16-2,27 (1H; m); 2,61 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 3,57 (3H; s); 4,13 (2H; d; J = 5,3 Hz); 4,36 (1H; brs); 6,97-7,02 (2H; m); 7,34-7,44 (1H; m).

2) El ácido 5-{[(terc-Butoxicarbonil)amino]metil}-4-(2,6-

difluorofenil)-6-isobutil-2-metilnicotínico (2,22 g; rendimiento 92%) fue obtenido como un sólido amarillo de metil 5-{[(terc-butoxicarbonil)amino]metil}-4-(2,6-difluorofenil)-6-isobutil-2-metilnicotinato (2,49 g; 5,55 mmol) según un método similar al método del Ejemplo 2-2).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,11-2,26 (1H; m); 2,64 (3H; s); 2,81 (2H; d; J = 7,2 Hz); 4,11-4,16 (2H; m); 4,37 (1H; brs); 6,96-7,01 (2H; m); 7,34-7,43 (1H; m).

3) El dihidrocloruro de ácido 5-(Aminometil)-4-(2,6-difluorofenil)-6-isobutil-2-metilnicotínico (185 mg, rendimiento 70%) fue obtenido como un sólido blanco de ácido 5-{[(terc-butoxicarbonil)amino]metil}-4-(2,6-difluorofenil)-6-isobutil-2-metilnicotínico (0,28 g, 0,635 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (CD_3OD) :1,08 (6H; d; J = 6,8 Hz); 2,19-2,29 (1H; m); 2,81-2,88 (3H; m); 2,98-3,08 (2H; m); 4,09-4,16 (2H; m); 7,20-7,27 (2H; m); 7,64-7,72 (1H; m).

Ejemplo 71

El terc-butil 5-(aminometil)-6-isobutil-2-metil-4-[4-(trifluorometil)fenil]nicotinato

1) Se obtuvieron 2-(3-Metilbutanoil)-3-[4-(trifluorometil)fenil]acrilonitrilo como un producto en bruto (9,8 g) de 5-metil-3-oxohexannitrilo (4,0 g; 32 mmol) y 4-(trifluorometil)benzaldehído (5,6 g; 32 mmol) según un método

similar al método del Ejemplo 29-1).

2) Terc-butil 5-ciano-6-isobutil-2-metil-4-[4-(trifluorometil)fenil]-1,4-dihidropiridin-3-carboxilato (4,8 g; rendimiento 36%) fue obtenido como polvo blanco del producto en bruto (9,8 g) obtenido en el 1) mencionado precedentemente y terc-butil 3-aminocrotonato (5,47 g, 35 mmol) según un método similar al método del Ejemplo 1-2). Es decir, se disolvieron el producto en bruto mencionado y terc-butil 3-aminocrotonato en metanol (200 mL) y la mezcla fue calentada bajo reflujo por 1 hr. La mezcla de reacción fue concentrada bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar terc-butil 5-ciano-6-isobutil-2-metil-4-[4-(trifluorometil)fenil]-1,4-dihidropiridin-3-carboxilato.

^{1}H-RMN ($CDCl_3$) δ:0,93 (3H; d; J = 6,6 Hz); 0,99 (3H; d; J = 6,5 Hz); 1,28 (9H; s); 1,75-2,00 (1H; m); 2,10-2,35 (2H; m); 2,36 (3H; s); 4,64 (1H; s); 5,60 (1H; brs); 7,36 (2H; d; J = 8,1 Hz); 7,56 (2H; d; J = 8,1 Hz).

Punto de fusión: 199-201°C

3) Terc-butil 5-ciano-6-isobutil-2-metil-4-[4-(trifluorometil)fenil]nicotinato (3,5 g; rendimiento 76%) fue obtenido como polvo blanco del terc-butil 5-ciano-6-isobutil-2-metil-4-[4-(trifluorometil)fenil]-1,4-dihidropiridin-3-carboxilato (4,7 g; 11 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,02 (6H; d; J = 6,6 Hz); 1,23 (9H; s); 2,20-2,40 (1H; m); 2,67 (3H; s); 2,95 (2H; d; J = 7,4 Hz); 7,51 (2H; d; J = 8,2 Hz); 7,76 (2H; d; J = 8,2 Hz).

Punto de fusión: 108-110°C

4) Terc-butil 5-(aminometil)-6-isobutil-2-metil-4-[4-(trifluorometil)fenil]nicotinato (3,3 g; rendimiento 96%) fue obtenido como polvo blanco del terc-butil 5-ciano-6-isobutil-2-metil-4-[4-(trifluorometil)fenil]nicotinato (3,5 g; 8,2 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,17 (9H; s); 1,38 (2H; brs); 2,15-2,35 (1H; m); 2,57 (3H; s); 2,80 (2H; d; J = 7,4 Hz); 3,60 (2H; s); 7,42 (2H; d; J = 8,0 Hz); 7,70 (2H; d; J = 8,0 Hz).

Punto de fusión: 88-90°C

Ejemplo 72

Hidrocloruro de ácido 5-(aminometil)-6-isobutil-2-metil-4-[4-(trifluorometil)fenil]nicotínico

5-(Aminometil)-6-isobutil-2-metil-4-[4-(trifluorometil)fenil]nicotínico (0,51 g; rendimiento 53%) fue obtenido como polvo blanco del terc-butil 5-(aminometil)-6-isobutil-2-metil-4-[4-(trifluorometil)fenil]nicotinato (1,0 g; 2,3 mmol) según un método similar al método del Ejemplo 24.

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,15-2,35 (1H;

m); 2,51 (3H; s); 2,78 (2H; d; J = 7,2 Hz); 3,75 (2H; s); 7,56 (2H; d; J = 8,0 Hz); 7,87 (2H; d; J = 8,0 Hz); 8,01 (2H; brs).

Ejemplo 73

Terc-butil 5-(aminometil)-6-isobutil-4-[4-(metoxicarbonil)fenil]-2-metilnicotinato

1) Metil 4-(2-ciano-5-metil-3-oxohex-1-en-1-il)benzoato fue obtenido como un producto en bruto (10,1 g) de 5-metil-3-oxohexannitrilo (4,0 g; 32 mmol) y metil 4-formilbenzoato (5,3 g; 32 mmol) según un método similar al método del Ejemplo 29-1).

2) Terc-butil 5-ciano-6-isobutil-4-[4-(metoxicarbonil)fenil]-2-metil-1,4-dihidropiridin-3-carboxilato (5,9 g; rendimiento 45%) fue obtenido como polvo blanco del producto en bruto (10.1 g) obtenido en el 1) mencionado precedentemente y terc-butil 3-aminocrotonato (5,25 g; 33 mmol) según un método similar al método del Ejemplo 1-2). Es decir, se disolvieron el producto en bruto mencionado y terc-butil 3-aminocrotonato en metanol (200 mL) y la mezcla fue calentada bajo reflujo por 2 hrs. La mezcla de reacción fue concentrada bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar terc-butil 5-ciano-6-isobutil-4-[4-(metoxicarbonil)fenil]-2-metil-1,4-dihidropiridin-3-carboxilato.

^{1}H-RMN ($CDCl_3$) δ:0,91 (3H; d; J = 6,6 Hz); 0,98 (3H; d; J =

6,6 Hz); 1,26 (9H; s); 1,75-2,00 (1H; m); 2,15-2,35 (2H; m); 2,36 (3H; s); 3,90 (3H; s); 4,63 (1H; s); 5,69 (1H; brs); 7,32 (2H; d; J = 8,3 Hz); 7,99 (2H; d; J = 8,3 Hz).

Punto de fusión: 191-193°C

3) Terc-butil 5-ciano-6-isobutil-4-[4-(metoxicarbonil)fenil]-2-metilnicotinato (5,4 g; rendimiento 95%) fue obtenido como polvo blanco del terc-butil 5-ciano-6-isobutil-4-[4-(metoxicarbonil)fenil]-2-metil-1,4-dihidropiridin-3-carboxilato (5,7 g; 14 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,6 Hz); 1,23 (9H; s); 2,20-2,35 (1H; m); 2,67 (3H; s); 2,94 (2H; d; J = 7,4 Hz); 3,96 (3H; s); 7,40-7,50 (2H; m); 8,10-8,20 (2H; m).

Punto de fusión: 108-109°C

4) Terc-butil 5-(aminometil)-6-isobutil-4-[4-(metoxicarbonil)fenil]-2-metilnicotinato (5,0 g; rendimiento 94%) fue obtenido como polvo blanco del terc-butil 5-ciano-6-isobutil-4-[4-(metoxicarbonil)fenil]-2-metilnicotinato (5,3 g; 13 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,17 (9H; s); 1,49 (2H; brs); 2,15-2,35 (1H; m); 2,57 (3H; s); 2,79 (2H; d; J = 7,2 Hz); 3,59 (2H; s); 3,96 (3H; s); 7,30-7,40 (2H; m); 8,05-8,15 (2H; m).

Punto de fusión: 77-81°C

Ejemplo 74

Hidrocloruro de ácido 5-(aminometil)-6-isobutil-4-[4-(metoxicarbonil)fenil]-2-metilnicotínico

El hidrocloruro de ácido 5-(aminometil)-6-isobutil-4-[4-(metoxicarbonil)fenil]-2-metilnicotínico (0,50 g; rendimiento 66%) fue obtenido como polvo blanco del terc-butil 5-(aminometil)-6-isobutil-4-[4-(metoxicarbonil)fenil]-2-metilnicotinato (0,80 g; 1,9 mmol) según un método similar al método del Ejemplo 24.

^{1}H-RMN (DMSO-d_6) δ:0,93 (6H; d; J = 6,6 Hz); 2,05-2,25 (1H; m); 2,41 (3H; s); 2,70 (2H; d; J = 7,0 Hz); 3,54 (2H; s); 3,88 (3H; s); 7,41 (2H; d; J = 8,1 Hz); 7,95 (2H; d; J = 8,1 Hz).

Ejemplo 75

Terc-butil 5-(aminometil)-4-(4-etilfenil)-6-isobutil-2-metilnicotinato

1) Fue obtenido 3-(4-etilfenil)-2-(3-metilbutanoil)acrilonitrilo como un producto en bruto (8,8 g) de 5-metil-3-oxohexannitrilo (4,0 g; 32 mmol) y 4-etilbenzaldehído (4,3 g; 32 mmol) según un método similar al método del Ejemplo 29-1).

2) Terc-butil 5-ciano-4-(4-etilfenil)-6-isobutil-2-metil-1,4-dihidropiridin-3-carboxilato (7,8 g; rendimiento 64%) fue obtenido como polvo blanco del producto en bruto (8,8 g)

obtenido en el 1) mencionado precedentemente y terc-butil 3-aminocrotonato (5,47 g; 35 mmol) según un método similar al método del Ejemplo 1-2). Es decir, se disolvieron el producto en bruto mencionado y terc-butil 3-aminocrotonato en metanol (200 mL) y la mezcla fue calentada bajo reflujo por 4 hrs. La mezcla de reacción fue concentrada bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de silice para dar terc-butil 5-ciano-4-(4-etilfenil)-6-isobutil-2-metil-1,4-dihidropiridin-3-carboxilato.

^{1}H-RMN ($CDCl_3$) δ:0,94 (3H; d; J = 6,5 Hz); 0,99 (3H; d; J = 6,5 Hz); 1,20 (3H; t; J = 7,6 Hz); 1,28 (9H; s); 1,80-2,00 (1H; m); 2,10-2,30 (2H; m); 2,32 (3H; s); 2,61 (2H; q; J = 7,6 Hz); 4,52 (1H; s); 5,55 (1H; brs); 7,10 (2H; d; J = 8,3 Hz), 7.14 (2H, d, J = 8,3 Hz).

Punto de fusión: 165-166°C

3) Terc-butil 5-ciano-4-(4-etilfenil)-6-isobutil-2-metilnicotinato (5,2 g; rendimiento 67%) fue obtenido como polvo blanco del terc-butil 5-ciano-4-(4-etilfenil)-6-isobutil-2-metil-1,4-dihidropiridin-3-carboxilato (7,8 g; 21 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,6 Hz); 1,23 (9H; s); 1,26 (3H; t; J = 7,6 Hz); 2,20-2,35 (1H; m); 2,64 (3H; s); 2,71 (2H; q; J = 7,6 Hz); 2,94 (2H; d; J = 7,4 Hz); 7,20-7,35

(4H; m).

Punto de fusión: 85-86°C

4) Terc-butil 5-(aminometil)-4-(4-etilfenil)-6-isobutil-2-metilnicotinato (7,0 g; rendimiento 97%) fue obtenido como polvo blanco del terc-butil 5-ciano-4-(4-etilfenil)-6-isobutil-2-metilnicotinato (7,2 g; 19 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,17 (9H; s); 1,25 (3H; t; J = 7,5 Hz); 1,38 (2H; brs); 2,15-2,30 (1H; m); 2,55 (3H; s); 2,69 (2H; q; J = 7,5 Hz); 2,78 (2H; d; J = 7,4 Hz); 3,63 (2H; s); 7,15 (2H; d; J = 7,9 Hz); 7,24 (2H; d; J = 7,9 Hz).

Punto de fusión: 50-52°C

Ejemplo 76

Hidrocloruro de ácido 5-(aminometil)-4-(4-etilfenil)-6-isobutil-2-metilnicotínico

El hidrocloruro de ácido 5-(Aminometil)-4-(4-etilfenil)-6-isobutil-2-metilnicotínico (0,52 g; rendimiento 79%) fue obtenido como polvo blanco del terc-butil 5-(aminometil)-4-(4-etilfenil)-6-isobutil-2-metilnicotinato (0,70 g; 1,8 mmol) según un método similar al método del Ejemplo 24.

^{1}H-RMN (DMSO-d_6) δ:0,95 (6H; d; J = 7,5 Hz); 1,23 (3H; t; J = 7,5 Hz); 2,10-2,30 (1H; m); 2,47 (3H; s); 2,67 (2H; q; J = 7,5 Hz); 2,77 (2H; d; J = 7,0 Hz); 3,74 (2H; s); 7,22 (2H; d;

J = 8,0 Hz); 7,30 (2H; d; J = 8,0 Hz); 8,81 (1H; brs).

Ejemplo 77

Metil 5-(aminometil)-4-(4-clorofenil)-2-etil-6-neopentilnicotinato

1) Metil 3-aminopent-2-enoato fue obtenido como un producto en bruto (20 g) de metil 3-oxopentanoato (13 g, 100 mmol) y acetato de amonio (38,5 g; 500 mmol) según un método similar al método del Ejemplo 12-1).

2) Metil 4-(4-clorofenil)-5-ciano-2-etil-6-neopentil-1,4-dihidropiridin-3-carboxilato (1,4 g; rendimiento 23%) fue obtenido como polvo amarillo de 5,5-dimetil-3-oxohexannitrilo (5,1 g; 32 mmol), 4-clorobenzaldehído (4;5 g; 32 mmol) y el producto en bruto (3,2 g) obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 1-2).

^{1}H-RMN ($CDCl_3$) δ:0,95-1,05 (3H; m); 1,01 (9H; s); 2,20 (1H; d; J = 13,8 Hz); 2,37 (1H; d; J = 13,8 Hz); 2,77 (2H; q; J = 7,5 Hz); 3,58 (3H; s); 4,60 (1H; s); 5,63 (1H; brs); 7,10-7,20 (2H; m); 7,25-7,30 (2H; m).

3) Metil 4-(4-clorofenil)-5-ciano-2-etil-6-neopentilnicotinato (0,58 g; rendimiento 43%) fue obtenido como polvo amarillo pálido de metil 4-(4-clorofenil)-5-ciano-2-etil-6-neopentil-1,4-dihidropiridin-3-carboxilato (1,4 g; 3,7 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,07 (9H; s); 1,33 (3H; t; J = 7,5 Hz); 2,87 (2H; q; J = 7,5 Hz); 3,03 (2H; s); 3,61 (3H; s); 7,25-7,35 (2H; m); 7,45-7,50 (2H; m).

Punto de fusión: 120-121°C

4) Metil 5-(aminometil)-4-(4-clorofenil)-2-etil-6-neopentilnicotinato (0,49 g; rendimiento 85%) fue obtenido como un aceite amarillo pálido de metil 4-(4-clorofenil)-5-ciano-2-etil-6-neopentilnicotinato (0,57 g, 1,5 mmol) según un método similar al método del Ejemplo 23-4).

^{1}H-RMN ($CDCl_3$) δ:1,03 (9H; s); 1,30 (3H; t; J = 7,5 Hz); 1,42 (2H; brs); 2,77 (2H; q; J = 7,5 Hz); 2,89 (2H; s); 3,51 (3H; s); 3,69 (2H; s); 7,15-7,25 (2H; m); 7,35-7,45 (2H; m).

Ejemplo 78

Dihidrocloruro de ácido 5-(aminometil)-4-(4-clorofenil)-2-etil-6-neopentilnicotínico

1) Metil 5-{[(terc-butoxicarbonil)amino]metil}-4-(4-clorofenil)-2-etil-6-neopentilnicotinato (0,52 g, rendimiento 97%) fue obtenido como polvo blanco de metil 5-(aminometil)-4-(4-clorofenil)-2-etil-6-neopentilnicotinato (0,42 g; 1,1 mmol) según un método similar al método del Ejemplo 2-1).

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,30 (3H; t; J = 7,5 Hz); 1,38 (9H; s); 2,78 (2H; q; J = 7,5 Hz); 2,87 (2H; s); 3,51 (3H; s); 4,18 (3H; brs); 7,10-7,20 (2H; m); 7,30-7,45 (2H; m).

2) El ácido 5-{[(terc-Butoxicarbonil)amino]metil}-4-(4-

clorofenil)-2-etil-6-neopentilnicotínico (0,37 g; rendimiento 81%) fue obtenido como polvo blanco de metil 5-{[(terc-butoxicarbonil)amino]metil}-4-(4-clorofenil)-2-etil-6-neopentilnicotinato (0,47 g; 0,99 mmol) según un método similar al método del Ejemplo 2-2).

^{1}H-RMN ($CDCl_3$) δ:1,01 (9H; s); 1,24 (3H; t; J = 7,4 Hz); 1,33 (9H; s); 2,73 (2H; q; J = 7,4 Hz); 2,73 (2H; s); 3,92 (2H; d; J = 4,5 Hz); 6,96 (1H; t; J = 4,5 Hz); 7,25-7,35 (2H; m); 7,47 (2H; d; J = 8,3 Hz); 13,05 (1H; brs).

Punto de fusión: 71-72°C

3) Dihidrocloruro de ácido 5-(Aminometil)-4-(4-clorofenil)-2-etil-6-neopentilnicotínico (0,24 g; rendimiento 83%) fue obtenido como polvo blanco de ácido 5-{[(terc-butoxicarbonil)amino]metil}-4-(4-clorofenil)-2-etil-6-neopentilnicotínico (0,30 g; 0,65 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,03 (9H; s); 1,26 (3H; t; J = 7,4 Hz); 2,79 (2H; q; J = 7,4 Hz); 2,90 (2H; brs); 3,83 (2H; d; J = 5,7 Hz); 7,36 (2H; d; J = 8,5 Hz); 7,50-7,60 (2H; m); 8,12 (3H; brs).

Punto de fusión: 230-235°C

Ejemplo 79

Terc-butil 5-(aminometil)-4-(4-clorofenil)-2-isopropil-6-neopentilnicotinato

1) Terc-butil 4-(4-clorofenil)-5-ciano-2-isopropil-6-neopentil-1,4-dihidropiridin-3-carboxilato (2,00 g; rendimiento 16%) fue obtenido como un sólido blanco de 5,5-dimetil-3-oxohexannitrilo (5,67 g; 36,7 mmol), 4-clorobenzaldehído (5,16 g; 36,7 mmol) y terc-butil 3-amino-4-metilpent-2-enoato (5,98 g; 30 mmol) según un método similar al método del Ejemplo 1-2).

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,04 (3H; d; J = 6,8 Hz); 1,21 (3H; d; J = 7,0 Hz); 1,28 (9H; s); 2,20 (1H; d; J = 13,9 Hz); 2,33 (1H; d; J = 14,1 Hz); 4,07-4,30 (1H; m); 4,55 (1H; s); 5,65 (1H; s); 7,16 (2H; d; J = 8,3 Hz); 7,22-7,35 (2H; m).

2) Terc-butil 4-(4-clorofenil)-5-ciano-2-isopropil-6-neopentilnicotinato (1,91 g; rendimiento 96%) fue obtenido como un sólido amarillo de terc-butil 4-(4-clorofenil)-5-ciano-2-isopropil-6-neopentil-1,4-dihidropiridin-3-carboxilato (2,00 g; 4,66 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,06 (9H; s); 1,27 (9H; s); 1,32 (6H; d; J = 6,6 Hz); 3,00 (2H; s); 3,13-3,25 (1H; m); 7,32 (2H; d; J = 8,5 Hz); 7,45 (2H; d; J = 8,5 Hz).

3) Terc-butil 5-(aminometil)-4-(4-clorofenil)-2-isopropil-6-neopentilnicotinato (1,24 g; rendimiento 67%) fue obtenido como un sólido blanco de terc-butil 4-(4-clorofenil)-5-ciano-2-isopropil-6-neopentilnicotinato (1,80 g; 4,27 mmol) según

un método similar al método del Ejemplo 23-4).

^{1}H-RMN ($CDCl_3$) δ:1,04 (9H; s); 1,21 (9H; s); 1,30 (6H; d; J = 6,6 Hz); 2,85 (2H; s); 3,01-3,16 (1H; m); 3,64 (2H; s); 7,22 (2H; d; J = 8,5 Hz); 7,40 (2H; d; J = 8,5 Hz).

Ejemplo 80

Dihidrocloruro de ácido 5-(aminometil)-4-(4-clorofenil)-2-isopropil-6-neopentilnicotínico

Dihidrocloruro de ácido 5-(Aminometil)-4-(4-clorofenil)-2-isopropil-6-neopentilnicotínico (393 mg, rendimiento 93%) fue obtenido como un sólido amarillo de terc-butil 5-(aminometil)-4-(4-clorofenil)-2-isopropil-6-neopentilnicotinato (406 mg; 0,941 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:1,04 (9H; s); 1,25 (6H; d; J = 6,8 Hz); 2,88 (2H; s); 3,05-3,14 (1H; m); 3,81 (2H; d; J = 5,3 Hz); 7,36 (2H; d; J = 8,5 Hz); 7,55 (2H; d; J = 8,5 Hz); 8,11 (3H; brs).

Ejemplo 81

Terc-butil 5-(aminometil)-4-(4-clorofenil)-6-isobutil-2-isopropilnicotinato

1) Terc-butil 4-(4-clorofenil)-5-ciano-6-isobutil-2-isopropil-1,4-dihidropiridin-3-carboxilato (6,18 g; rendimiento 50%) fue obtenido como un sólido amarillo de 5-metil-3-oxohexannitrilo (4,14 g; 33 mmol), 4-

clorobenzaldehído (4,64 g; 33 mmol) y terc-butil 3-amino-4-metilpent-2-enoato (5,98 g; 30 mmol) según un método similar al método del Ejemplo 1-2).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; dd; J = 8,5; 6,8 Hz); 1,14 (3H; d; J = 7,0 Hz); 1,22 (3H; d; J = 7,0 Hz); 1,28 (9H; s); 1,81-1,98 (1H; m); 2,25 (2H; d; J = 7,4 Hz); 4,09-4,26 (1H; m); 4,55 (1H; s); 5,71 (1H; s); 7,15 (2H; d; J = 8,3 Hz); 7,25-7,27 (2H; m).

2) Terc-butil 4-(4-clorofenil)-5-ciano-6-isobutil-2-isopropilnicotinato (6,10 g; rendimiento 99%) fue obtenido como un aceite amarillo de terc-butil 4-(4-clorofenil)-5-ciano-6-isobutil-2-isopropil-1,4-dihidropiridin-3-carboxilato (6,16 g; 14,8 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,6 Hz); 1,26 (9H; s); 1,32 (6H; d; J = 6,8 Hz); 2,22-2,39 (1H; m); 2,95 (2H; d; J = 7,2 Hz); 3,19-3,25 (1H; m); 7,33 (2H; d; J = 8,7 Hz); 7,46 (2H; d; J = 8,7 Hz).

3) Terc-butil 5-(aminometil)-4-(4-clorofenil)-6-isobutil-2-isopropilnicotinato (5,52 g, rendimiento 89%) fue obtenido como un sólido blanco de terc-butil 4-(4-clorofenil)-5-ciano-6-isobutil-2-isopropilnicotinato (6,10 g; 1,48 mmol) según un método similar al método del Ejemplo 23-4).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,8 Hz); 1,21 (9H; s); 1,30

(6H; d; J = 6,8 Hz); 2,23-2,39 (1H; m); 2,78 (2H; d; J = 7,2 Hz); 3,01-3,16 (1H; m); 3,59 (1H; s); 7,22 (2H; d; J = 8,5 Hz); 7,39 (2H; d; J = 8,5 Hz).

Ejemplo 82

Dihidrocloruro de ácido 5-(aminometil)-4-(4-clorofenil)-6-isobutil-2-isopropilnicotínico

El dihidrocloruro de ácido 5-(Aminometil)-4-(4-clorofenil)-6-isobutil-2-isopropilnicotínico (263 mg, rendimiento 62%) fue obtenido como un sólido amarillo del terc-butil 5-(aminometil)-4-(4-clorofenil)-6-isobutil-2-isopropilnicotinato (404 mg; 0,969 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 1,25 (6H; d; J = 6,8 Hz); 2,20-2,39 (1H; m); 2,83 (2H; d; J = 7,0 Hz); 3,01-3,19 (1H; m); 3,77 (2H; d; J = 5,3 Hz); 7,36 (2H; d; 8,5 Hz); 7,55 (2H; d; J = 8,3 Hz); 8,14 (3H; brs).

Ejemplo 83

Terc-butil 5-(aminometil)-4-(4-clorofenil)-2,6-diisobutilnicotinato

1) Terc-butil 3-amino-5-metilhex-2-enoato fue obtenido como un producto en bruto (20,2 g) del ácido de Meldrum (17,3 g; 120 mmol) y cloruro de isovalerilo (15,8 mL; 132 mmol) según un método similar al método del Ejemplo 25-1).

2) Terc-butil 4-(4-clorofenil)-5-ciano-2,6-diisobutil-1,4-dihidropiridin-3-carboxilato (10,2 g; rendimiento 72%) fue

obtenido como polvo amarillo pálido de 5-metil-3-oxohexannitrilo (4,1 g; 33 mmol), 4-clorobenzaldehído (4,6 g; 33 mmol) y el producto en bruto (10,1 g) obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 1-2).

^{1}H-RMN ($CDCl_3$) δ:0,95-1,05 (12H; m); 1,29 (9H; s); 1,80-2,05 (2H; m); 2,15-2,35 (2H; m); 2,55-2,70 (2H; m); 4,60 (1H; s); 5,51 (1H; brs); 7,15-7,25 (2H; m); 7,25-7,30 (2H; m).

Punto de fusión: 166-168°C

3) Terc-butil 4-(4-clorofenil)-5-ciano-2,6-diisobutilnicotinato (9,6 g; rendimiento 99%) fue obtenido como polvo blanco de terc-butil 4-(4-clorofenil)-5-ciano-2,6-diisobutil-1,4-dihidropiridin-3-carboxilato (9,8 g; 23 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:0,95 (6H; d; J = 6,8 Hz); 1,00 (6H; d; J = 6,6 Hz); 1,25 (9H; s); 2,15-2,40 (2H; m); 2,76 (2H; d; J = 7,2 Hz); 2,95 (2H; d; J = 7,4 Hz); 7,30-7,35 (2H; m); 7,40-7,50 (2H; m).

4) Terc-butil 5-(aminometil)-4-(4-clorofenil)-2,6-diisobutilnicotinato (0,97 g, rendimiento 96%) fue obtenido como polvo blanco de terc-butil 4-(4-clorofenil)-5-ciano-2,6-diisobutilnicotinato (1,0 g; 2,3 mmol) según un método similar al método del Ejemplo 23-4).

^{1}H-RMN ($CDCl_3$) δ:0,94 (6H; d; J = 6,6 Hz); 0,98 (6H; d; J =

6,6 Hz); 1,20 (9H; s); 1,48 (2H; brs); 2,15-2,35 (2H; m); 2,67 (2H; d; J = 7,4 Hz); 2,80 (2H; d; J = 7,4 Hz); 3,61 (2H; s); 7,20-7,25 (2H; m); 7,35-7,45 (2H; m).

Ejemplo 84

Dihidrocloruro de ácido 5-(aminometil)-4-(4-clorofenil)-2,6-diisobutilnicotínico

Dihidrocloruro de ácido 5-(aminometil)-4-(4-clorofenil)-2,6-diisobutilnicotínico (0,92 g, rendimiento 98%) fue obtenido como polvo blanco de terc-butil 5-(aminometil)-4-(4-clorofenil)-2,6-diisobutilnicotinato (0,90 g; 2,1 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:0,90 (6H; d; J = 6,6 Hz); 0,97 (6H; d; J = 6,6 Hz); 2,10-2,35 (2H; m); 2,66 (2H; d; J = 6,4 Hz); 2,84 (2H; d; J = 6,2 Hz); 3,79 (2H; d; J = 5,5 Hz); 7,36 (2H; d; J = 8,5 Hz); 7,50-7,60 (2H; m); 8,17 (3H; brs).

Punto de fusión: 205°C (descompuesto)

Ejemplo 85

Terc-butil 5-(aminometil)-4-(4-clorofenil)-2-isobutil-6-neopentilnicotinato

1) Terc-butil 4-(4-clorofenil)-5-ciano-2-isobutil-6-neopentil-1,4-dihidropiridin-3-carboxilato fue obtenido como un producto en bruto (7,9 g) de 5,5-dimetil-3-oxohexannitrilo (4,6 g; 33 mmol), 4-clorobenzaldehído (4,6 g; 33 mmol) y el producto en bruto (10,1 g) de terc-butil 3-amino-5-metilhex-2-enoato obtenido en Ejemplo 83-1), según un método similar

al método del Ejemplo 1-2).

2) Terc-butil 4-(4-clorofenil)-5-ciano-2-isobutil-6-neopentilnicotinato (5,5 g; rendimiento 37%) fue obtenido como polvo blanco del producto en bruto (7,9 g) obtenido en el 1) mencionado precedentemente según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:0,95 (6H; d; J = 6,6 Hz); 1,06 (9H; s); 1,26 (9H; s); 2,20-2,35 (1H; m); 2,76 (2H; d; J = 7,2 Hz); 3,01 (2H; s); 7,30-7,35 (2H; m); 7,40-7,50 (2H; m).

3) Terc-butil 5-(aminometil)-4-(4-clorofenil)-2-isobutil-6-neopentilnicotinato (4,5 g; rendimiento 86%) fue obtenido como polvo amarillo del terc-butil 4-(4-clorofenil)-5-ciano-2-isobutil-6-neopentilnicotinato (5,2 g; 12 mmol) según un método similar al método del Ejemplo 23-4).

^{1}H-RMN ($CDCl_3$) δ:0,93 (6H; d; J = 6,8 Hz); 1,02 (9H; s); 1,20 (9H; s); 1,86 (2H; brs); 2,15-2,35 (1H; m); 2,67 (2H; d; J = 7,4 Hz); 2,87 (2H; s); 3,71 (2H; s); 7,20-7,25 (2H; m); 7,35-7,45 (2H; m).

<u>Ejemplo 86</u>

Dihidrocloruro de ácido 5-(aminometil)-4-(4-clorofenil)-2-isobutil-6-neopentilnicotínico

El dihidrocloruro de ácido 5-(aminometil)-4-(4-clorofenil)-2-isobutil-6-neopentilnicotínico (0,29 g; rendimiento 56%) fue obtenido como polvo blanco del terc-

butil 5-(aminometil)-4-(4-clorofenil)-2-isobutil-6-neopentilnicotinato (0,50 g; 1,1 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:0,90 (6H; d; J = 6,6 Hz); 1,02 (9H; s); 2,15-2,30 (1H; m); 2,66 (2H; q; J = 7,2 Hz); 2,91 (2H; s); 3,84 (2H; d; J = 5,5 Hz); 7,30-7,40 (2H; m); 7,50-7,60 (2H; m); 8,12 (3H; brs).

Punto de fusión: 251°C (descompuesto)

Ejemplo 87

Dihidrocloruro de [5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetonitrilo

1) Terc-butil {[5-(hidroximetil)-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (4,5 g; rendimiento 48%) fue obtenido como polvo blanco de metil 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilnicotinato (10 g; 22,7 mmol) según un método similar al método del Ejemplo 5-1).

^{1}H-RMN ($CDCl_3$) δ:1,01 (9H; s); 1,37 (9H; s); 2,41 (3H; s); 2,67 (3H; s); 2,84 (2H; s); 4,10 (2H; d; J = 4,9 Hz); 4,16 (1H; s); 4,36 (2H; d; J = 5,7 Hz); 7,05 (2H; d; J = 8,1 Hz); 7,26 (2H; d; J = 8,1 Hz).

2) Una mezcla de terc-butil {[5-(hidroximetil)-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (0,9 g; 2,2 mmol), trietilamina (0,4 g; 4,0 mmol) y

tetrahidrofurano (30 mL) fue enfriada a 0°C y cloruro de metansulfonilo (0,3 g; 2,6 mmol) fue agregado por gotas. Después de agitar a temperatura ambiente por 30 min., la mezcla de reacción fue vertida en carbonato hidrógeno de sodio acuoso saturado. La mezcla se extrajo con acetato de etilo y el extracto fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida para dar metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metilo (0.85 g, rendimiento 79%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:1,01 (9H; s); 1,37 (9H; s); 2,41 (3H; s); 2,67 (3H; s); 2,75 (3H; s); 2,86 (2H; s); 4,11 (2H; d; J = 4,9 Hz); 4,17 (1H; s); 4,91 (2H; s); 7,04 (2H; d; J = 8,1 Hz); 7,27 (2H; d; J = 8,1 Hz).

3) El metansulfonato de [5-{[(terc-Butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metilo (0,84 g; 1,7 mmol) fue disuelto en dimetilsulfóxido (10 mL) y fue agregado cianuro de potasio (0,14 g; 2,0 mmol). La mezcla fue agitada a 60°C por 1 hr. Fue agregado acetato de etilo a la mezcla de reacción, y la mezcla fue lavada consecutivamente con agua y solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice para

dar terc-butil {[5-(cianometil)-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (0,45 g, rendimiento 63%) como un polvo.

^{1}H-RMN ($CDCl_3$) δ:1,01 (9H; s); 1,37 (9H; s); 2,43 (3H; s); 2,65 (3H; s); 2,85 (2H; s); 3,30 (2H; s); 4,11 (2H; d; J = 4,5 Hz); 4,17 (1H; s); 7,05 (2H; d; J = 8,0 Hz); 7,30 (2H; d; J = 8,0 Hz).

4) Dihidrocloruro de [5-(Aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetonitrilo (0,28 g; 76%) fue obtenido como polvo de terc-butil {[5-(cianometil)-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (0,4 g; 0,95 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,01 (9H; s); 2,42 (3H; s); 2,76 (3H; s); 3,06 (2H; s); 3,59 (2H; s); 3,80 (2H; d; J = 5,3 Hz); 7,24 (2H; d; J = 7,9 Hz); 7,42 (2H; d; J = 7,9 Hz); 8,20 (3H; s).

Ejemplo 88

Dihidrocloruro de 2-[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetamida

1) Terc-butil {[5-(2-amino-2-oxoetil)-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (0,3 g; 82%) fue obtenido como polvo de terc-butil {[5-(cianometil)-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (0,35 g; 0,83 mmol) según un método

similar al método del Ejemplo 6-1).

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,37 (9H; s); 2,40 (3H; s); 2,56 (3H; s); 2,84 (2H; s); 3,30 (2H; s); 4,10 (2H; d; J = 4,9 Hz); 4,19 (1H; s); 5,15 (1H; s); 5,20 (1H; s); 7,00 (2H; d; J = 7,9 Hz); 7,24 (2H; d; J = 7,9 Hz).

2) El dihidrocloruro de 2-[5-(Aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetamida (0,18 g; 85%) fue obtenido como polvo de terc-butil {[5-(2-amino-2-oxoetil)-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (0,22 g; 0,5 mmol) según un método similar al método del Ejemplo 6-2).

^{1}H-RMN (DMSO-d_6) δ:1,03 (9H; s); 2,41 (3H; s); 2,77 (2H; s); 3,29 (3H; s); 3,87 (2H; s); 4,28 (2H; s); 7,03 (1H; s); 7,20 (2H; d; J = 7,8 Hz); 7,38 (2H; d; J = 7,8 Hz); 7,39 (1H; s); 8,24 (3H; s).

Ejemplo 89

Dihidrocloruro del acetato de [5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metilo

1) Una mezcla de terc-butil {[5-(hidroximetil)-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (0,3 g; 0,73 mmol), trietilamina (0,1 g; 1,0 mmol) y tetrahidrofurano (20 mL) fue enfriada a 0°C y cloruro de acetilo (0,06 g; 0,8 mmol) fue agregado por gotas. Después de agitar a temperatura ambiente por 30 min., la mezcla de

reacción fue vertida en carbonato hidrógeno de sodio acuoso saturado. La mezcla se extrajo con acetato de etilo y el extracto fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida para dar acetato de [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metilo (0,26 g; rendimiento 76%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,37 (9H; s); 2,00 (3H; s); 2,40 (3H; s); 2,57 (3H; s); 2,85 (2H; s); 4,11 (2H; d; J=4,9 Hz); 4,17 (1H; s); 4,76 (2H; s); 7,00 (2H; d; J = 8,1 Hz); 7,22 (2H; d; J = 8,1 Hz).

2) El dihidrocloruro del acetato de [5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metilo (99 mg, 90%) fue obtenido como polvo del acetato de [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metilo (0,12 g; 0,26 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,02 (9H; s); 1,96 (3H; s); 2,40 (3H; s); 2,78 (3H; s); 3,14 (2H; s); 3,82 (2H; s); 4,72 (2H; s); 7,21 (2H; d; J = 7,8 Hz); 7,36 (2H; d; J = 7,8 Hz); 8,23 (3H; s).

Ejemplo 90

Dihidrocloruro de {[2-isobutil-6-metil-4-(4-metilfenil)-5-({[4-(metiltio)fenil]tio}metil)piridin-3-il]metil}amina

1) Una mezcla de terc-butil {[5-(hidroximetil)-2-isobutil-

6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (3,06 g; 7,68 mmol), trietilamina (1,8 mL; 12,9 mmol) y tetrahidrofurano (30 mL) fue enfriada a 0°C, y fue agregado cloruro de metansulfonilo (0,89 mL; 11,5 mmol) por gotas. Después de agitar a temperatura ambiente por 30 min., la mezcla de reacción fue vertida en carbonato hidrógeno de sodio acuoso saturado, y la mezcla se extrajo con acetato de etilo. El extracto fue secado sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida para dar metansulfonato [5-({[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilo como un producto en bruto. El producto en bruto fue disuelto en N,N-dimetilformamida (30 mL). El carbonato de potasio (1,77 g; 12,8 mmol) y fue agregado 4-(metiltio)benzentiol (1,00 g; 6,40 mmol) y la mezcla fue agitada con calentamiento a 50°C por 1 hr. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar terc-butil {[2-isobutil-6-metil-4-(4-metilfenil)-5-({[4-(metiltio)fenil]tio}metil)piridin-3-il]metil}carbamato (3,43 g, rendimiento 99%) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,15-

2,24 (1H; m); 2,40 (3H; s); 2,45 (3H; s); 2,63 (3H; s); 2,75 (2H; d; J = 7,4 Hz); 3,75 (2H; s); 4,02 (2H; d; J = 5,1 Hz); 4,18 (1H; brs); 6,98 (2H; d; J = 8,1 Hz); 7,03 (2H; d; J = 8.7 Hz), 7.08 (2H, d, J = 8,7 Hz); 7,20 (2H, d, J = 7,9 Hz).

2) El dihidrocloruro de {[2-isobutil-6-metil-4-(4-metilfenil)-5-({[4-(metiltio)fenil]tio}metil)piridin-3-il]metil}amina (380 mg, rendimiento 79%) fue obtenido como un sólido amarillo del terc-butil {[2-isobutil-6-metil-4-(4-metilfenil)-5-({[4-(metiltio)fenil]tio}metil)piridin-3-il]metil}carbamato (508 mg; 0,947 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,13-2,22 (1H; m); 2,40 (3H; s); 2,46 (3H; s); 2,78 (3H; s); 3,11 (2H; brs); 3,76 (2H; d; J = 4,5 Hz); 3,87 (2H; s); 7,12 (2H; d; J = 8,7 Hz); 7,16 (2H; d; J = 8,7 Hz); 7,22 (2H; d; J = 7,9 Hz); 7,33 (2H, d, J = 7.9 Hz), 8.38 (3H, brs).

Ejemplo 91

Dihidrocloruro de {[2-isobutil-6-metil-4-(4-metilfenil)-5-({[4-(metilsulfonil)fenil]sulfonil}metil)piridin-3-il]metil}amina

1) A una solución de terc-butil {[2-isobutil-6-metil-4-(4-metilfenil)-5-({[4-(metiltio)fenil]tio}metil)piridin-3-il]metil}carbamato (1,10 g; 2,05 mmol) en metanol (15 mL), agua (1,5 mL) y tetrahidrofurano (1,5 mL) fue agregado ácido sulfúrico (121 mg; 1,23 mmol) y "Oxone" (marca de fábrica,

3,78 g; 6,15 mmol) y la mezcla fue agitada a la temperatura ambiente por 2 hrs. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y fue lavada consecutivamente con carbonato hidrógeno de sodio acuoso saturado y la solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El sólido blanco obtenido fue lavado con diisopropil éter para dar terc-butil {[2-isobutil-6-metil-4-(4-metilfenil)-5-({[4-(metilsulfonil)fenil]sulfonil}metil)piridin-3-il]metil}carbamato (1,06 g; rendimiento 86%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,8 Hz); 1,38 (9H; s); 2,17-2,27 (1H; m); 2,42 (3H; s); 2,70 (3H; s); 2,78 (2H; d; J = 7,2 Hz); 3,09 (3H; s); 4,00 (2H; d; J = 5,1 Hz); 4,19 (1H; brs); 4,36 (2H; s); 6,87 (2H; d; J = 7,9 Hz); 7,19 (2H; d; J = 7,9 Hz); 7,69 (2H; d; J = 8,3 Hz); 8,00 (2H; d; J = 8,5 Hz).

2) El dihidrocloruro de {[2-isobutil-6-metil-4-(4-metilfenil)-5-({[4-(metilsulfonil)fenil]sulfonil}metil)piridin-3-il]metil}amina (480 mg, rendimiento 98%) fue obtenido como polvo blanco del terc-butil {[2-isobutil-6-metil-4-(4-metilfenil)-5-({[4-(metilsulfonil)fenil]sulfonil}metil)piridin-3-il]metil}carbamato (511 mg; 0,851 mmol) según un método

similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,17-2,27 (1H; m); 2,38 (3H; s); 2,81 (3H; brs); 3,00 (2H; brs); 3,34 (3H; s); 3,68 (2H; brs); 7,03 (2H; d; J = 7,4 Hz); 7,22 (2H; d; J = 7,9 Hz); 7,77 (2H; d; J = 7,0 Hz); 8,11 (2H; d; J = 8,5 Hz); 8,26 (3H, brs).

Ejemplo 92

Dihidrocloruro de (6-metil-4-(4-metilfenil)-5-{[(4-metil-4H-1,2,4-triazol-3-il)tio]metil}-2-neopentilpiridin-3-il)metilamina

1) Terc-butil [(6-metil-4-(4-metilfenil)-5-{[(4-metil-4H-1,2,4-triazol-3-il)tio]metil}-2-neopentilpiridin-3-il)metil]carbamato (0,28 g; 77%) fue obtenido como polvo de metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metilo (0.35 g, 0.71 mmol) y 4-metil-4H-1,2,4-triazol-3-tiol (99 mg; 0,86 mmol) según un método similar al método del Ejemplo 33-1).

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,37 (9H; s); 2,39 (3H; s); 2,65 (3H; s); 2,84 (2H; s); 3,41 (3H; s); 4,07 (2H; d; J = 5,3 Hz); 4,17 (3H; s); 7,02 (2H; d; J = 7,9 Hz); 7,22 (2H; d; J = 7,9 Hz); 8,08 (1H; s).

2) El dihidrocloruro de (6-metil-4-(4-metilfenil)-5-{[(4-metil-4H-1,2,4-triazol-3-il)tio]metil}-2-neopentilpiridin-3-il)metilamina (0,12 g; 72%) fue obtenido como polvo del terc-

butil [(6-metil-4-(4-metilfenil)-5-{[(4-metil-4H-1,2,4-triazol-3-il)tio]metil}-2-neopentilpiridin-3-il)metil]carbamato (0,18 g; 0,35 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,02 (9H; s); 2,39 (3H; s); 2,80 (3H; s); 3,19 (2H; s); 3,41 (3H; s); 3,79 (2H; s); 4,05 (2H; s); 7,13 (2H; d; J = 8,1 Hz); 7,35 (2H; d; J = 8,1 Hz); 8,25 (3H; s); 8,74 (1H; s).

Ejemplo 93

Dihidrocloruro de {6-metil-4-(4-metilfenil)-2-neopentil-5-[(1,3-tiazol-2-iltio)metil]piridin-3-il}metilamina

1) Terc-butil ({6-metil-4-(4-metilfenil)-2-neopentil-5-[(1,3-tiazol-2-iltio)metil]piridin-3-il}metil)carbamato (0.25 g, 69%) fue obtenido como polvo de metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metilo (0,35 g; 0,71 mmol) y 2-mercaptotiazol (100 mg; 0,86 mmol) según un método similar al método del Ejemplo 33-1).

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,37 (9H; s); 2,38 (3H; s); 2,64 (3H; s); 2,84 (2H; s); 4,08 (2H; d; J = 5,1 Hz); 4,17 (3H; s); 7,03 (2H; d; J = 7,9 Hz); 7,18 (1H; d; J = 3,4 Hz); 7,20 (2H; d; J = 7,9 Hz); 7,60 (1H; d; J = 3,4 Hz).

2) El dihidrocloruro de {6-metil-4-(4-metilfenil)-2-neopentil-5-[(1,3-tiazol-2-iltio)metil]piridin-3-

il}metilamina (0,11 g; 80%) fue obtenido como polvo de terc-butil ({6-metil-4-(4-metilfenil)-2-neopentil-5-[(1,3-tiazol-2-iltio)metil]piridin-3-il}metil)carbamato (0,15 g; 0,29 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,01 (9H; s); 2,38 (3H; s); 2,78 (3H; s); 3,10 (2H; s); 3,78 (2H; s); 4,20 (2H; s); 7,20 (2H; d; J = 8,1 Hz); 7,33 (2H; d; J = 8,1 Hz); 7,69 (1H; d; J = 3,4 Hz); 7,71 (1H; d; J = 3,4 Hz); 8,17 (3H; s).

Ejemplo 94

Dihidrocloruro de 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinonitrilo

1) A una solución (20 mL) de terc-butil {[5-(aminocarbonil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1.750 mg; 4,2 mmol) en diclorometano fue agregado trietilamina (1,2 mL; 8,4 mmol), y fue agregado anhidrido trifluorometansulfónico (780 mL; 8,4 mmol) por gotas bajo efriamiento con hielo. La mezcla fue agitada por 30 min. y la mezcla de reacción fue lavada consecutivamente con agua y solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar terc-butil {[5-ciano-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1.130 mg, rendimiento 68%) como cristales blancos.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,40 (9H; s); 2,20-2,29 (1H; m); 2,43 (3H; s); 2,77 (3H; s); 2,83 (2H; d; J = 9,0 Hz); 4,18 (2H; s); 4,20 (1H; brs); 7,13 (2H; d; J = 6,0 Hz); 7,31 (2H; d; J = 6,0 Hz).

2) El dihidrocloruro de 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinonitrilo (81 mg, rendimiento 88%) fue obtenido como polvo blanco del terc-butil {[5-ciano-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (100 mg; 0,25 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,95 (6H; d; J = 6,6 Hz); 2,21-2,27(1H; m); 2,42 (3H; s); 2,71 (3H; s); 2,89 (2H; d; J = 6,9 Hz); 3,82 (2H; d; J = 5,4 Hz); 7,33-7,40 (4H; m); 8,50 (3H; brs).

Ejemplo 95

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]urea

1) A una solución (3 mL) de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) en N,N-dimetilformamida fue agregado trietilamina (170 µl; 1,5 mmol), y fue agregado difenilfosforil azida (260 µL; 1,5 mmol) por gotas bajo efriamiento con hielo. La mezcla fue agitada por 30 min. y fue agregada agua a la mezcla de reacción. La mezcla se extrajo con acetato de etilo, y la

capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue disuelto en tolueno (3 mL). La mezcla fue calentada bajo reflujo con agitación durante 1 hr. Fue agregado 25% amonio acuoso (3 mL) a la mezcla de reacción y la mezcla fue agitada a 100°C por 1 hr. Fue agregada agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar el terc-butil {[5-[(aminocarbonil)amino]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (101 mg, rendimiento 24%) como cristales blancos.

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,15-2,26 (1H; m); 2,39 (3H; s); 2,56 (3H; s); 2,76 (2H; d; J = 7,2 Hz); 4,10 (2H; d; J = 5,1 Hz); 4,24 (1H; brs); 4,38 (2H; s); 5,50 (1H; s); 7,01 (2H; d; J = 7,5 Hz); 7,24 (2H; d; J = 7,5 Hz).

2) dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]urea (84 mg, rendimiento 92%) fue obtenido como polvo blanco de terc-butil {[5-[(aminocarbonil)amino]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (100 mg; 0,23 mmol)

según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 5,4 Hz); 2,14-2,19 (1H; m); 2,40 (3H; s); 2,53 (3H; s); 3,0, (2H; brs); 3,80 (2H; brs); 3,83 (1H; brs); 5,94 (1H; brs); 7,20 (2H; d; J = 7,8Hz); 7,36 (2H; d; J = 7,8 Hz); 8,28 (3H; brs).

Ejemplo 96

Dihidrocloruro de N'-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-N,N-dimetilurea

1) Terc-butil {[5-{[(dimetiamino)carbonil]amino}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (158 mg, rendimiento 35%) fue obtenido como polvo blanco de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y 2M solución de tetrahidrofurano de dimetilamina (0,6 mL; 1,2 mmol) según un método similar al método del Ejemplo 95-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,15-2,25 (1H; m); 2,41 (3H; s); 2,51 (3H; s); 2,71 (6H; s); 2,75 (2H; d; J = 9,0 Hz); 4,08 (2H; d; J = 5,1 Hz); 4,23 (1H; brs); 5,32 (1H; s); 7,02 (2H; d; J = 7,8 Hz); 7,24 (2H; d; J = 7,8 Hz).

2) Dihidrocloruro de N'-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-N,N-dimetilurea (108 mg, rendimiento 73%) fue obtenido como polvo blanco del terc-butil {[5-{[(dimetilamino)carbonil]amino}-2-isobutil-6-metil-

4-(4-metilfenil)piridin-3-il]metil}carbamato (158 mg; 0,35 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,3 Hz); 2,17-2,20 (1H; m); 2,39 (3H; s); 2,64 (9H; s); 3,09 (2H; brs); 3,83 (2H; brs); 7,20 (2H; d; J = 7,8 Hz); 7,31 (2H; d; J = 7,8 Hz); 7,86 (1H; brs); 8,39 (3H; brs).

Ejemplo 97

Dihidrocloruro de bencil [5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbamato

1) Bencil [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbamato (1.600 mg, rendimiento 35%) fue obtenido como polvo blanco de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (3700 mg; 8,9 mmol) y alcohol bencílico (2,3 mL; 10,7 mmol) según un método similar al método del Ejemplo 95-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,13-2,16 (1H; m); 2,39 (3H; s); 2,51 (3H; s); 2,75 (2H; d; J = 7,2 Hz); 4,08 (2H; s); 4,22 (1H; brs); 5,07 (2H; s); 5,70 (1H; brs); 6,95 (2H; brs); 7,17 (2H; d; J = 7,8 Hz); 7,20-7,26 (2H; m); 7,31-7,36 (3H; m).

2) Dihidrocloruro de bencil [5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbamato (54 mg, rendimiento 76%) fue obtenido como polvo blanco del bencil

[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbamato (75 mg; 0,14 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,3 Hz); 2,15-2,22 (1H; m); 2,39 (3H; s); 2,56 (3H; s); 2,99 (2H; s); 3,79 (2H; s); 5,00 (2H; s); 7,14-7,18 (4H; m); 7,29-7,35 (5H; m); 8,29 (3H; brs); 9,08 (1H; brs).

Ejemplo 98

Trihidrocloruro de 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)-3-piridinamina

1) A una solución (100 mL) de bencil [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbamato (1500 mg; 2,9 mmol) en etanol fue agregado 5% paladio-carbono (150 mg) y la mezcla fue agitada bajo una atmósfera de hidrógeno a temperatura ambiente por 2 hrs. La mezcla de reacción fue filtrada y el filtrado fue concentrado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel de silice para dar el terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1000 mg, rendimiento 90%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,94 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,09-2,16 (1H; m); 2,41 (3H; s); 2,42 (3H; s); 2,65 (2H; d; J = 7,2 Hz); 3,28 (2H; s); 4,02 (2H; brs); 4,22 (1H; brs); 7,06

(2H; d; J = 8,1 Hz); 7,29 (2H; d; J = 7,7 Hz).

2) Trihidrocloruro de 5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)-3-piridinamina (34 mg, rendimiento 62%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (50 mg; 0,13 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DOSO-d_6) δ:0,94 (6H; d; J = 6,6 Hz); 1,97-2,08 (1H; m); 2,42 (3H; s); 2,65 (3H; s); 2,99 (2H; s); 3,69 (2H; s); 5,40 (3H; brs); 7,26 (2H; d; J = 8,1Hz); 7,44 (2H; d; J = 8,1 Hz); 8,38 (3H; brs).

Ejemplo 99

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metansulfonamida

A una solución de terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (100 mg; 0,26 mmol) en tetrahidrofurano (2 mL) fue agregado trietilamina (54 µL; 0,39 mmol) y cloruro de metansulfonilo (30 µL; 0,39 mmol) fue agregado a temperatura ambiente. Entonces la mezcla fue agitada por 3 hrs. Fue agregado agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo

obtenido fue purificado por cromatografía en columna de gel de sílice para dar un aceite. A una solución del aceite en el acetato de etilo (1 mL) fue agregado solución 4N de ácido clorhídrico acetato de etilo (1 mL) y la mezcla fue agitada a la temperatura ambiente por 1 hr. El solvente fue evaporado bajo presión reducida y el residuo obtenido se cristalizó del hexano para dar dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metansulfonamida (25 mg, rendimiento 22%) como un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,18-2,24 (1H; m); 2,20 (3H; s); 2,39 (3H; s); 2,71 (3H; s); 2,96 (2H; s); 3,79 (2H; s); 7,28 (2H; d; J = 6,9Hz); 7,34 (2H; d; J = 6,9 Hz); 8,32 (3H; brs); 9,27 (1H; brs).

Ejemplo 100

Dihidrocloruro de N-[5-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}sulfonil)-4-metil-1,3-tiazol-2-il]acetamida

Dihidrocloruro de N-[5-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}sulfonil)-4-metil-1,3-tiazol-2-il]acetamida (58 mg, rendimiento 39%) fue obtenido como polvo blanco del cloruro de terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (100 mg; 0,26 mmol) y 2-(acetilamino)-4-metil-1,3-tiazol-5-sulfonilo (76 mg; 0,3 mmol) según un

método similar al método del Ejemplo 99.

^{1}H-RMN (DMSO-d_6) δ:0,94 (6H; d; J = 6,6 Hz); 2,02 (3H; s); 2,19 (3H; s); 2,18-2,23 (1H; m); 2,27 (3H; s); 2,53 (3H; s); 2,84 (2H; brs); 3,69 (2H; brs); 6,92-6,97 (4H; m); 8,10 (3H; brs); 9,89 (1H; brs).

Ejemplo 101

Trihidrocloruro de {[5-(aminometil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}amina

1) Una mezcla de terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,16 g; 2,91 mmol), trietilamina (0,8 mL; 5,82 mmol) y tetrahidrofurano (15 mL) fue enfriada a 0°C y fue agregado por gotas cloruro de metansulfonilo (500 mg; 4,37 mmol). Después de agitar a temperatura ambiente por 30 min., la mezcla de reacción fue vertida en carbonato hidrógeno de sodio acuoso saturado, y la mezcla se extrajo con acetato de etilo. El extracto fue secado sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida para dar metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilo como un producto en bruto. El producto bruto fue disuelto en N,N-dimetilformamida (30 mL) y fue agregado azida de sodio (379 mg; 5,82 mmol). La mezcla fue agitada a 80°C por 30 min. La mezcla de reacción fue diluida con acetato de etilo (100 mL) y fue lavada con

solución salina saturada. La capa orgánica fue secada sobre sulfato de magnèsio anhidro y el solvente fue evaporado bajo presión reducida para dar un residuo. Una mezcla del residuo obtenido, 10% paladio-carbono (304 mg, 0.291 mmol) y etanol (15 mL) fueron agitados bajo atmósfera de hidrógeno a la temperatura ambiente por 2 hrs. Después de la filtración, el solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de silice para dar terc-butil {[5-(aminometil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (690 mg, rendimiento 60%) como un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 1,41 (2H; brs); 2,14-2,23 (1H; m); 2,41 (3H; s); 2,64 (3H; s); 4,02 (2H; d; J = 5,1 Hz); 4,18 (1H; brs); 7,02 (2H; d; J = 7,9 Hz); 7,25 (2H; d; J = 7,0 Hz).

2) Trihidrocloruro de {[5-(Aminometil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}amina (204 mg, rendimiento 99%) fue obtenido como polvo blanco del terc-butil {[5-(aminometil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (200 mg; 0,503 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,13-2,24 (1H; m); 2,43 (3H; s); 2,50 (3H; s); 2,98 (2H; brs); 3,76 (4H; brs); 7,34-7,45 (4H; m); 8,51 (6H; brs),

Ejemplo 102

Dihidrocloruro de N-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}-4-(metilsulfonil)bencensulfonamida

1) A una solución (10 mL) de terc-butil {[5-(aminometil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (290 mg; 0,729 mmol) y trietilamina (0,15 mL; 1,09 mmol) en tetrahidrofurano fue agregado cloruro de 4-(metilsulfonil)bencensulfonilo (223 mg; 0,875 mmol) y la mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue diluida con acetato de etilo (100 mL) y fue lavada consecutivamente con carbonato hidrógeno de sodio acuoso saturado y solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el sólido amarillo obtenido fue lavado con diisopropil éter para dar el terc-butil ({2-isobutil-6-metil-4-(4-metilfenil)-5-[({[4-(metilsulfonil)fenil]sulfonil}amino)metil]piridin-3-il}metil)carbamato (391 mg, rendimiento 87%) como un polvo amarillo.

^{1}H-RMN ($CDCl_3$) δ:0,95 (6H; d; J = 6,6 Hz); 1,36 (9H; s); 2,13-2,22 (1H; m); 2,41 (3H; s); 2,61 (3H; s); 2,73 (2H; d; J = 7,4 Hz); 3;08 (3H; s); 3;83 (2H; d; J = 5;8 Hz); 3;97 (2H; d; J = 4;9 Hz); 4;11-4;20 (2H; m); 6;84 (2H; d; J = 8;1 Hz); 7;13 (2H; d; J = 7;7 Hz); 7,77 (2H; d; J = 8,7 Hz); 7,98 (2H;

d; J = 8,5 Hz).

2) Dihidrocloruro de N-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}-4-(metilsulfonil)bencensulfonamida (370 mg, rendimiento 99%) fue obtenido como polvo amarillo del terc-butil ({2-isobutil-6-metil-4-(4-metilfenil)-5-[({[4-(metilsulfonil)fenil]sulfonil}amino)metil]piridin-3-il}metil)carbamato (391 mg; 0,635 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,11-2,19 (1H; m); 2,35 (3H; s); 2,50 (3H; s); 2,70-2,82 (2H; m); 3,31 (3H; s); 3,66 (2H; brs); 3,72 (2H; brs); 7,11-7,21 (4H; m); 7,83 (2H; dd; J = 8,3; 1,3 Hz); 8,08 (2H; d; J = 8,1 Hz); 8,31 (3H; brs).

Ejemplo 103

Trihidrocloruro de etilo ({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}amino)acetato.

1) A una solución de metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilo (300 mg; 0,63 mmol) en tetrahidrofurano (5 mL) fue agregado trietilamina (223 µL; 1,6 mmol) y hidrocloruro de glicin etil éster (100 mg; 0,7 mmol) y la mezcla fue agitada a 60°C durante 3 días. Fue agregado agua a la mezcla de reacción, y la mezcla se extrajo

con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar el acetato de etil({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}amino) (185 mg, rendimiento 61%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,95 (6H; d; J = 6,6 Hz); 1,22 (3H; t; J = 6,9Hz); 1,38 (9H; s); 2,15-2,22 (1H; m); 2,41 (3H; s); 2,67 (3H; s); 2;73 (2H; d; J = 7;2Hz); 3;18 (2H; s); 3;43 (2H; s); 4;02 (2H; s); 4;09 (2H; q; J = 6;9Hz); 4;18 (1H; brs); 7;03 (2H; d; J =7,8Hz); 7,25 (2H; d; J = 7,8 Hz),

2) El trihidrocloruro de etil({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}amino)acetato (57 mg, rendimiento 95%) fue obtenido como polvo blanco del etil({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}amino)acetato (60 mg; 0,12 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 1,18 (3H; t; J = 6,9 Hz); 2,11-2;24 (1H; m); 2;42 (3H; s); 2;92 (3H; brs); 3;03 (2H; brs); 3;61 (2H; s); 3;72 (2H; brs); 4;06 (2H; s); 4;08 (2H; q; J = 6;9 Hz); 7;35 (2H; d; J =8;1Hz); 7;40 (2H; d; J = 8,1 Hz); 8,43 (3H; brs).

Ejemplo 104

Trihidrocloruro de ácido ({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}amino)acetico

1) A una solución de etil ({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}amino)acetato (100 mg; 0,2 mmol) en etanol (3 mL) fue agregada una solución 8N de hidróxido de sodio acuoso (3 mL) y la mezcla fue agitada a 80°C por 15 hrs. Ácido clorhídrico 1N fue agregado para neutralizar la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida para dar ácido ({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}amino)acético (92 mg, rendimiento 99%) como un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ:0,91 (6H; d; J = 6,3 Hz); 1,35 (9H; s); 2,11-2,24 (1H; m); 2,36 (3H; s); 2,54 (2H; s); 2,57 (3H; s); 2,97 (2H; s); 3,39 (2H; s); 3,76 (2H; s); 6,78 (1H; brs); 7,18 (2H; d; J =7,8Hz); 7,22 (2H; d; J = 7,8 Hz).

2) Trihidrocloruro de ácido ({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}amino)acético (75 mg, rendimiento 80%) fue obtenido como polvo blanco de ácido ({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-

4-(4-metilfenil)piridin-3-il]metil}amino)acético (90 mg; 0,2 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,14-2,21 (1H; m); 2,42 (3H; s); 2,89 (3H; s); 3,01 (2H; brs); 3,52 (2H; s); 3,72 (2H; s); 4,04 (2H; s); 7,35 (2H; d; J =8,1 Hz); 7,39 (2H; d; J = 8,1 Hz); 8,37 (3H; brs); 9,29 (1H; brs).

Ejemplo 105

Trihidrocloruro de 4-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}-2-piperazinona

1) Terc-butil ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(3-oxo-1-piperazinil)metil]piridin-3-il}metil)carbamato (78 mg, rendimiento 77%) fue obtenido como polvo blanco de metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilo (300 mg; 0,63 mmol) y 2-piperazinona (65 mg; 0,65 mmol) según un método similar al método del Ejemplo 103-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,14-2,23 (1H; m); 2,49 (5H; s); 2,64 (3H; s); 2,73 (2H; d; J = 7,2Hz); 2,89 (2H; s); 3,22 (2H; brs); 3,28 (2H; s); 4,01 (2H; d; J = 5,1Hz); 4,20 (1H; brs); 5,69 (1H; brs); 6,96 (2H; d; J = 7,8 Hz); 7,21 (2H; d; J = 7,8 Hz).

2) Trihidrocloruro de 4-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}-2-piperazinona (64 mg, rendimiento 87%) fue obtenido como polvo blanco del terc-

butil ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(3-oxo-1-piperazinil)metil]piridin-3-il}metil)carbamato (75 mg, 0.15 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 1,91 (2H; s); 2,09-2,14 (1H; m); 2,42 (3H; s); 3,00 (3H; brs); 3,18 (4H; brs); 3,75 (2H; brs); 7,30 (2H; d; J = 7,5 Hz); 7,41 (2H; d; J = 7,5 Hz); 7,41 (1H; brs); 8,52 (3H; brs).

Ejemplo 106

Dihidrocloruro de 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}-2,4-imidazolidindiona

1) A una solución de terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (100 mg; 0,25 mmol), hidantoína (38 mg; 0,38 mmol) y tributilfosfina (95 mL; 0,38 mmol) en tetrahidrofurano (3 mL) fue agregado 1,1'-(azodicarbonil)dipiperidina (96 mg; 0,38 mmol) y la mezcla fue agitada a la temperatura ambiente por 4 hrs. La mezcla de reacción fue concentrada y los materiales insolubles fueron eliminados por filtración. El filtrado fue purificado por cromatografía en columna de gel de sílice para dar terc-butil {[5-[(2,5-dioxo-1-imidazolidinil)metil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (68 mg, rendimiento 57%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,95 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,11-2,26 (1H; m); 2,39 (3H; s); 2,55 (3H; s); 2,73 (2H; d; J =

7,5 Hz); 3,77 (2H; s); 3,99 (2H; d; J = 5,1 Hz); 4,23 (1H; brs); 4,46 (2H; s); 5,10 (1H; brs); 7,07 (2H; d; J = 7,8 Hz); 7,23 (2H; d; J = 7,8 Hz).

2) Dihidrocloruro de 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}-2,4-imidazolidinediona (54 mg, rendimiento 95%) fue obtenido como polvo blanco de terc-butil {[5-[(2,5-dioxo-1-imidazolidinil)metil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,14-2,19 (1H; m); 2,37 (3H; s); 2,84 (3H; s); 3,11 (2H; brs); 3,71 (4H; s); 4,35 (2H; s); 7,18 (2H; d; J = 8,1 Hz); 7,33 (2H; d; J = 7,8 Hz); 8,00 (1H; brs); 8,30 (1H; brs).

Ejemplo 107

Dihidrocloruro de 1-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}-2,5-piperazindiona

1) A una solución de Z-glicina (1,2 g; 6 mmol) y N,N-dimetilformamida (10 µl) en tetrahidrofurano (5 mL) fue agregado cloruro de oxalilo (530 µL, 6 mmol), y la mezcla fue agitada a la temperatura ambiente por 30 min. A la mezcla de reacción fueron agregados por gotas a una solución de etil ({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}amino)acetato (1,4 g; 3 mmol), piridina (970 mL, 12 mmol) y 4-dimetilaminopiridina (5

mg) en tetrahidrofurano (10 mL) bajo efriamiento con hielo y la mezcla fue agitada por 3 hrs. Fue agregado agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el aceite obtenido fue disuelto en etanol (10 mL). Fue agregado 5% paladio-carbono (100 mg) y la mezcla fue agita bajo atmósfera de hidrógeno a la temperatura ambiente por 2 hrs. La mezcla de reacción fue filtrada y el filtrado fue concentrado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar el terc-butil {[5-[(2,5-dioxo-1-piperazinil)metil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (35 mg, rendimiento 2,4%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,18-2,24 (1H; m); 2,40 (3H; s); 2,51 (3H; s); 2,76 (2H; d; J = 7,5Hz); 3,47 (2H; s); 3,93 (2H; s); 4,03 (2H; d; J = 5,1 Hz); 4,24 (1H; brs); 4,51 (2H; s); 5,88 (1H; brs); 6,98 (2H; d; J = 7,5 Hz); 7,25 (2H; d; J = 7,5 Hz).

2). Dihidrocloruro de 1-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}-2,5-piperazindiona (14 mg, rendimiento 60%) fue obtenida como polvo blanco del terc-butil {[5-[(2,5-dioxo-1-piperazinil)metil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato según un

método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,15-2,19 (1H; m); 2,39 (3H; s); 2,69 (3H; s); 3,25 (2H; s); 3,67 (2H; s); 3,73 (2H; brs); 4,31 (2H; s); 7,18 (2H; d; J = 8,1 Hz); 7,37 (2H; d; J = 7,8 Hz); 8,06 (1H; brs); 8,24 (3H; brs).

Ejemplo 108

Dihidrocloruro de {[2-isobutil-4-(4-metilfenil)-6-fenilpiridin-3-il]metil}amina

1) A una solución (140 mL) de acetofenona (8,40 g, 70 mmol) y p-tolualdehído (8,40 g; 70 mmol) en etanol fue agregado hidróxido de sodio (7,0 g; 175 mmol) y la mezcla fue agitada durante 3 días. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el sólido amarillo obtenido fue lavado con diisopropil éter para dar (2E)-3-(4-metilfenil)-1-fenilprop-2-en-1-ona (9,12 g; rendimiento 59%) como un polvo amarillo.

^{1}H-RMN ($CDCl_3$) δ:2,40 (3H; s); 7,23 (2H; d; J = 8,1 Hz); 7,47-7,62 (6H; m); 7,80 (1H; d; J = 15,8 Hz); 8,00-8,03 (2H; m).

2) Una mezcla de 5-metil-3-oxohexannitrilo (5,0 g; 40 mmol); ácido acético (2,3 mL; 40 mmol); acetato de amonio (15,4 g; 200 mmol) y tolueno (250 mL) fue calentada bajo reflujo usando una trampa Dean-Stark por 12 hrs. A la mezcla

de reacción se le permitió enfriar a la temperatura ambiente, fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida para dar un residuo (4,5 g). El residuo (2,25 g) fue disuelto en etanol (100 mL) y (2E)-3-(4-metilfenil)-1-fenilprop-2-en-1-ona (3,69 g; 16,6 mmol) y fue agregado hidróxido de sodio (0,8 g; 20 mmol). La mezcla fue calentada bajo reflujo por 3 hrs. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y lavada con cloruro de amonio acuoso saturado. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar 2-isobutil-4-(4-metilfenil)-6-fenilnicotinonitrilo (2,68 g, rendimiento 49%) como un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ:1,07 (6H; d; J = 6,8 Hz); 2,35-2,48 (4H; m); 3,06 (2H; d; J = 7,2 Hz); 7,35 (2H; d; J = 7,9 Hz); 7,49-7,56 (5H; m); 7,67 (1H; s); 8,07-8,13 (1H; m).

3) La {[2-isobutil-4-(4-metilfenil)-6-fenilpiridin-3-il]metil}amina (1,70 g, rendimiento 63%) fue obtenida como un aceite amarillo de 2-isobutil-4-(4-metilfenil)-6-fenilnicotinonitrilo (2,65 g; 8,12 mmol) según un método similar al método del Ejemplo 1-4). El aceite fue disuelto en solución 4N ácido clorhídrico 1,4-dioxano (20 mL) y el solvente fue evaporado bajo presión reducida. El sólido

amarillo obtenido fue lavado con diisopropil éter para dar dihidrocloruro. de {[2-isobutil-4-(4-metilfenil)-6-fenilpiridin-3-il]metil}amina (1,99 g, rendimiento 96%) como un polvo amarillo.

^{1}H-RMN (DMSO-d_6) δ:1,03 (6H; d; J = 6,6 Hz); 2,34-2,41 (4H; m); 2,94 (2H; d; J = 7,0 Hz); 4,00 (2H; d; J = 5,5 Hz); 7,36 (2H; d; J = 8,2 Hz); 7,41 (2H; d; J = 8,3 Hz); 7,47-7,54 (3H; m); 7,70 (1H; s); 8,15 (2H; dd; J = 7,9; 1,5 Hz); 8,43 (3H; brs).

Ejemplo 109

Maleato de ácido 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico

El ácido 5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,50 g; 4,80 mmol) fue disuelto en un solvente mezcla de agua (15 mL) y acetonitrilo (15 mL) y la mezcla fue calentada bajo reflujo por 10 min. El ácido maleico (558 mg; 4,80 mmol) fue agregado a la solución obtenida y la mezcla fue agitada a la misma temperatura por 10 min. El acetonitrilo (200 mL) fue agregado a la solución obtenida, y a la mezcla se le permitió enfriar a la temperatura ambiente y fue agitada a 0°C por 30 min. El sólido precipitado fue recolectado por filtración y fue lavado con acetonitrilo (30 mL) para dar el maleato de ácido 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (667 mg, rendimiento 32%) como un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,18-2,27 (1H; m); 2,37 (3H; s); 2,74 (2H; d; J = 7,0 Hz); 3,79 (2H; s); 6,01 (2H; s); 7,19 (2H; d; J = 7,9 Hz); 7,29 (2H; d; J = 7,5 Hz).

Ejemplo 110

dihidrocloruro de ácido 5-(aminometil)-6-(metoximetil)-2-metil-4-(4-metilfenil)nicotínico

1) Una solución (40 mL) de metil 4-metoxiacetoacetato (5,85 g; 40 mmol), p-tolualdehído (4,81 g; 40 mmol), piperidina (340 mg, 4 mmol) y ácido acético (240 mg, 4 mmol) en isopropanol fue agitada a temperatura ambiente durante 3 días. El solvente fue evaporado bajo presión reducida para dar un residuo. El 3-metil 5-terc-butil 2-(metoximetil)-6-metil-4-(4-metilfenil)-1,4-dihidropiridin-3,5-dicarboxilato (5,85 g; rendimiento 50%) fue obtenido como un aceite amarillo del residuo obtenido y terc-butil 3-aminocrotonato (4,71 g, 30,0 mol) según un método similar al método del Ejemplo 1-2). Es decir, se disolvieron el residuo mencionado y terc-butil 3-aminocrotonato en metanol (30 mL) y la mezcla fue calentada bajo reflujo por 1,5 hrs. La mezcla de reacción fue concentrada bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar 3-metil 5-terc-butil 2-(metoximetil)-6-metil-4-(4-metilfenil)-1,4-dihidropiridin-3,5-dicarboxilato.

^{1}H-RMN ($CDCl_3$) δ:1,40 (9H; s); 2,28 (3H; s); 2,32 (3H; s);

3,45-3,46 (3H; m); 3,62-3,63 (3H; m); 4,55-4,76 (2H; m); 4,89-4,95 (1H; m); 6,94 (1H; brs); 7,01 (2H; d; J = 7,7 Hz); 7,15 (2H; d; J = 8,1 Hz).

2) El 3-metil 5-terc-butil 2-(metoximetil)-6-metil-4-(4-metilfenil)piridin-3,5-dicarboxilato (3,78 g, rendimiento 65%) fue obtenido como un aceite amarillo del 3-metil 5-terc-butil 2-(metoximetil)-6-metil-4-(4-metilfenil)-1,4-dihidropiridin-3,5-dicarboxilato (5,85 g; 15,1 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,23 (9H; s); 2,37 (3H; s); 2,61 (3H; s); 3,36 (3H; s); 3,54 (3H; s); 4,66 (2H; s); 7,13-7,15 (2H; m); 7,17-7,19 (2H; m).

3) Una suspensión de 3-metil 5-terc-butil 2-(metoximetil)-6-metil-4-(4-metilfenil)piridin-3,5-dicarboxilato (3,78 g, 9,81 mmol) en tolueno (50 mL) fue enfriada a -78°C y fue agregada unas solución 1,50 M de hidruro de diisobutilaluminio tolueno (25 mL; 24,5 mmol) por gotas durante 15 min. La mezcla fue agitada a -78°C por 30 min., se permitió calentar hasta 0°C y adicionalmente fue agitada por 10 min. El metanol (0,5 mL) fue agregado a la mezcla de reacción y fue agregado sulfato de sodio 10 hidrato (8,1 g; 9,8 mmol). La mezcla fue agitada a la temperatura ambiente por 1 hr. El material insoluble fue filtrado y el filtrado fue concentrado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice para

dar terc-butil 5-(hidroximetil)-6-(metoximetil)-2-metil-4-(4-metilfenil)nicotinato (810 mg, rendimiento 23%) como un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ:1,21 (9H; s); 2,39 (3H; s); 2,59 (3H; s); 3,50 (3H; s); 4,39 (2H; d; J = 6,8 Hz); 4,76 (2H; s); 7,21 (4H; s).

4) Una mezcla de terc-butil 5-(hidroximetil)-6-(metoximetil)-2-metil-4-(4-metilfenil)nicotinato (810 mg; 2,27 mmol), trietilamina (0,63 mL; 4,54 mmol) y tetrahidrofurano (30 mL) fue enfriada a 0°C y fue agregado cloruro de metansulfonilo (0,26 mL; 3,40 mmol) por gotas. Después de agitar a temperatura ambiente por 30 min., la mezcla de reacción fue diluída con acetato de etilo (100 mL) y fue lavada con carbonato hidrógeno de sodio acuoso saturado. La capa orgánica fue secada sobre sulfato de magnesio anhidro, y el solvente fue evaporado bajo presión reducida. El residuo fue disuelto en N,N-dimetilformamida (20 mL) y fue agregado azida de sodio (296 mg; 4,54 mmol). La mezcla fue agitada a 80°C por 1 hr. Fue agregado acetato de etilo a la mezcla de reacción, y la mezcla fue lavada consecutivamente con agua y solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida. Una mezcla del residuo, 10% paladio-carbono (242 mg; 0,227 mmol) y etanol (30 mL) fueron agitados bajo atmósfera de hidrógeno a la temperatura

ambiente por 30 min. Después de la filtración, el solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar terc-butil 5-(aminometil)-6-(metoximetil)-2-metil-4-(4-metilfenil)nicotinato (600 mg, rendimiento 74%) como un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ:1,19 (9H; s); 2,40 (3H; s); 2,57 (3H; s); 3,48 (3H; s); 3,63 (2H; s); 4,69 (2H; s); 7,12 (2H; d; J = 8,1 Hz); 7,23 (2H; d; J = 7,7 Hz),

5) Dihidrocloruro de ácido 5-(Aminometil)-6-(metoximetil)-2-metil-4-(4-metilfenil)nicotínico (533 mg, rendimiento 84%) fue obtenido como polvo blanco del terc-butil 5-(aminometil)-6-(metoximetil)-2-metil-4-(4-metilfenil)nicotinato (600 mg; 1,69 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:2,37 (3H; s); 2,53 (3H; s); 3,41 (3H; s); 3,86 (2H; d; J = 5,7 Hz); 4,76 (2H; s); 7,24 (2H; d; J = 8,1 Hz); 7,30 (2H; d; J = 8,1 Hz); 8,10 (3H; brs),

Ejemplo 111

Trihidrocloruro de ácido 5,6-bis(aminometil)-2-metil-4-(4-metilfenil)nicotínico

1) El etil 3-amino-4-[(terc-butoxicarbonil)amino]but-2-enoato (5,37g, rendimiento 99%) fue obtenido como un aceite amarillo de etil 4-[(terc-butoxicarbonil)amino]-3-

oxobutanoato (5,4 g; 22,0 mmol) según un método similar al método del Ejemplo 108-2).

^{1}H-RMN ($CDCl_3$) δ:1,26 (3H; t; J = 7,2 Hz); 1,46 (9H; s); 3,77 (2H; d; J = 6,6 Hz); 4,12 (2H; q; J = 7,1 Hz); 4,55 (1H; s).

2) Una mezcla de terc-butil acetoacetato (4,75 g; 30 mmol), p-tolualdehído (4,51 g; 37,5 mmol), piperidina (0,30 mL; 3,00 mmol) y etanol (0,2 mL) fue agitada a temperatura ambiente durante un día. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo obtenido y etil 3-amino-4-[(terc-butoxicarbonil)amino]but-2-enoato (5,37 g; 22,0 mmol) fueron agitados a 80°C por 30 min. y además fue agitado a 130°C por 3 hrs. La mezcla obtenida fue purificada por cromatografía en columna de gel de sílice para dar el 5-terc-butil 3-etil 2-{[(terc-butoxicarbonil)amino]metil}-6-metil-4-(4-metilfenil)-1,4-dihidropiridin-3,5-dicarboxilato (1,95 g; rendimiento 18%) como un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ:1,22-1,28 (3H; m); 1,40 (9H; s); 1,46 (9H; s); 2,27 (6H; s); 4,04-4,18 (3H; m); 4,37-4,44 (1H; m); 4,87 (1H; s); 5,35 (1H; brs); 7,01 (2H; d; J = 7,9 Hz); 7,15 (2H; d; J = 8,1 Hz).

3) El 3-etil 5-terc-butil 2-{[(terc-

butoxicarbonil)amino]metil}-6-metil-4-(4-metilfenil)piridin-3,5-dicarboxilato (1,94 g; rendimiento 99%) fue obtenido como un aceite amarillo del 3-etil 5-terc-butil 2-{[(terc-butoxicarbonil)amino]metil}-6-metil-4-(4-metilfenil)-1,4-dihidropiridin-3,5-dicarboxilato (1,95 g; 4.01 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:0,93 (3H; t; J = 7,2 Hz); 1,23 (9H; s); 1,47 (9H; s); 2,37 (3H; s); 2,61 (3H; s); 4,02 (2H; q; J = 7,1 Hz); 4,50 (2H; d; J = 4,7 Hz); 5,87 (1H; brs); 7,13 (2H; d; J = 8,3 Hz); 7,17 (2H; d; J = 8,3 Hz).

4) Terc-butil 6-{[(terc-butoxicarbonil)amino]metil}-5-(hidroximetil)-2-metil-4-(4-metilfenil)nicotinato (1,45 g; rendimiento 82%) fue obtenido como un aceite amarillo del 3-etil 5-terc-butil 2-{[(terc-butoxicarbonil)amino]metil}-6-metil-4-(4-metilfenil)piridin-3,5-dicarboxilato (1,94 g; 4,00 mmol) según un método similar al método del Ejemplo 110-3).

^{1}H-RMN ($CDCl_3$) δ:1,20 (9H; s); 1,46 (9H; s); 2,39 (3H; s); 2,57 (3H; s); 3,38 (1H; brs); 4,46 (2H; d; J = 6,0 Hz); 4,54 (2H; d; J = 5,8 Hz); 5,87 (1H; brs); 7,18 (2H; d; J = 8,3 Hz); 7,21 (2H; d; J = 8,3 Hz).

5) Terc-butil 5-(aminometil)-6-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)nicotinato (580 mg, rendimiento 40%) fue obtenido como polvo blanco del terc-butil 6-{[(terc-

butoxicarbonil)amino]metil}-5-(hidroximetil)-2-metil-4-(4-metilfenil)nicotinato (1,45 g; 3,28 mmol) según un método similar al método del Ejemplo 110-4).

^{1}H-RMN ($CDCl_3$) δ:1,18 (9H; s); 1,49 (9H; s); 2,39 (3H; s); 2,56 (3H; s); 3,62 (2H; s); 4,58 (2H; d; J = 4,7 Hz); 6,22 (1H; brs); 7,10 (2H; d; J = 8,1 Hz); 7,22 (2H; d; J = 7,9 Hz).

6) Trihidrocloruro de ácido 5,6-Bis(aminometil)-2-metil-4-(4-metilfenil)nicotínico (510 mg, rendimiento 99%) fue obtenido como un sólido amarillo del terc-butil 5-(aminometil)-6-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)nicotinato (580 mg; 1,31 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:2,37 (3H; s); 2,57 (3H; s); 3,84-3,89 (2H; m); 4,51-4,61 (2H; m); 7,23 (2H; d; J = 7,9 Hz); 7,31 (2H; d; J = 7,9 Hz); 8,42 (3H; brs); 8,54 (3H; brs).

Ejemplo 112

Hidrocloruro de ácido 5-(aminometil)-6-hidroxi-2-metil-4-(4-metilfenil)nicotínico

1) Una mezcla de terc-butil acetoacetato (4,75 g, 30 mmol), p-tolualdehído (4,51 g; 37,5 mmol), piperidina (0,30 mL; 3,00 mmol) y etanol (0,2 mL) fue agitado a temperatura ambiente durante un día. La mezcla de reacción fue diluida con acetato de etilo (100 mL) y lavada con solución salina saturada. La

capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo obtenido, cianoacetato de etilo (6,79 g; 60,0 mmol) y acetato de amonio (11,6 g; 150 mmol) fueron agitados a 140°C por 3 hrs. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y lavada con carbonato hidrógeno de sodio acuoso saturado. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar terc-butil 5-ciano-6-hidroxi-2-metil-4-(4-metilfenil)nicotinato (0,87 g; rendimiento 9%) como un sólido blanco.

^{1}H-RMN ($CDCl_3$) δ:1,19 (9H; s); 2,41 (3H; s); 2,57 (3H; s); 7,24-7,31 (4H; m).

2) Terc-butil 5-(aminometil)-6-hidroxi-2-metil-4-(4-metilfenil)nicotinato fue obtenido como un sólido blanco del terc-butil 5-ciano-6-hidroxi-2-metil-4-(4-metilfenil)nicotinato (0,50 g; 1,54 mmol) según un método similar al método del Ejemplo 1-4). Subsiguientemente, terc-butil 5-{[(terc-butoxicarbonil)amino]metil}-6-hidroxi-2-metil-4-(4-metilfenil)nicotinato (210 mg, rendimiento 32%) fue obtenido como un aceite incoloro según un método similar al método del Ejemplo 2-1).

^{1}H-RMN ($CDCl_3$) δ:1,13 (9H; s); 1,39 (9H; s); 2,38 (3H; s);

2,43 (3H; s); 4,02 (2H; d; J = 5,8 Hz); 7,10 (2H; d; J = 7,9 Hz); 7,22 (2H; d; J = 7,9 Hz); 12,39 (1H; brs).

3) El hidrocloruro de ácido 5-(Aminometil)-6-hidroxi-2-metil-4-(4-metilfenil)nicotínico (167 mg, rendimiento 99%) fue obtenido como un sólido blanco del terc-butil 5-{[(terc-butoxicarbonil)amino]metil}-6-hidroxi-2-metil-4-(4-metilfenil)nicotinato (210 mg, 0.490 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN (DMSO-d_6) δ:2,33 (3H; s); 2,35 (3H; s); 3,51 (2H; s); 7,15 (2H; d; J = 7,9 Hz); 7,26 (2H; d; J = 7,9 Hz); 7,94 (3H; brs); 12,42 (1H; s); 12,74 (1H; s).

Ejemplo 113

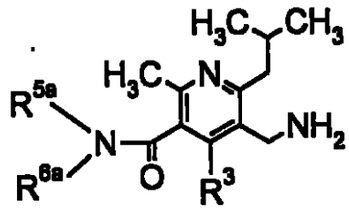
Ditrifluoroacetato de 5-(aminometil)-N;6-diisobutil-2-metil-4-(4-metilfenil)nicotinamida

El ácido 5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (23,9 mg; 0,06 mmol), isobutilamina (5,3 mg; 0,072 mmol), 1-hidroxi-1H-benzotriazol (11,0 mg; 0,072 mmol) e hidrocloruro de 1-etil-3-(3-dimetilaminopropil)carbodiimida (13,8 mg; 0,072 mmol) fue disuelto en una mezcla de solvente de N,N-dimetilformamida (1,25 mL) con diclorometano (0,4 mL), y la mezcla fue agitada a 50°C durante 2 días. La mezcla de reacción fue diluída con diclorometano (3 mL) y fue lavada consecutivamente con carbonato hidrógeno de sodio acuoso saturado (0,5 mL) y solución salina saturada (0,5 mL). El

ácido trifluoracético (2 mL) fue agregado a la capa orgánica y la mezcla fue agitada por 2 hrs. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por HPLC preparativa para dar ditrifluoroacetato de 5-(aminometil)-N,6-diisobutil-2-metil-4-(4-metilfenil)nicotinamida (22.4 mg, rendimiento 63%) como un aceite amarillo.

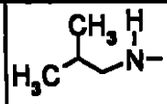
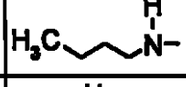
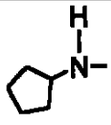
EIMS (M+1): 368

Fueron sintetizados los compuestos de Ejemplos 114-168 de los ácidos nicotínico y amina que corresponden a las Tablas 1-4 siguientes según un método similar al método del Ejemplo 113. Fueron obtenidos los compuestos de los Ejemplos 162-164 en forma libre neutralizando el trifluoroacetato de amida nicotínica resultante con carbonato hidrógeno de sodio acuoso saturado.



□E, g,

Tabla 1

Ejemplo	-NR^{5a}R^{6a}	-R^3	EIMS (M+1)	HA
113		4-Me-Fenilo	368	2CF$_3$COOH
114		4-Me-Fenilo	368	2CF$_3$COOH
115		4-Me-Fenilo	380	2CF$_3$COOH

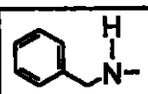
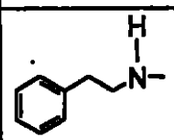
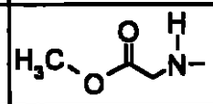
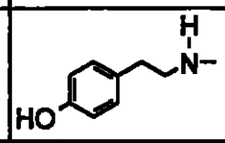
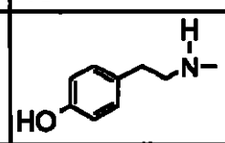
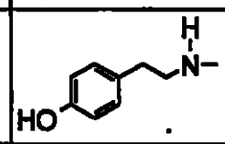
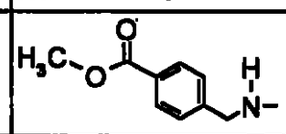
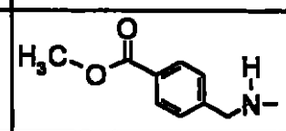
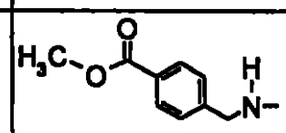
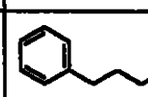
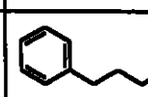
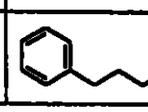
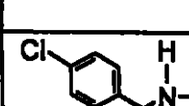
116		4-Me-Fenilo	402	$2CF_3COOH$
117		4-Me-Fenilo	416	$2CF_3COOH$
118		4-Me-Fenilo	384	$2CF_3COOH$
119		4-Me-Fenilo	432	$2CF_3COOH$
120		4-F-Fenilo	436	$2CF_3COOH$
121		2,6-di-F-Fenilo	454	$2CF_3COOH$
122		4-Me-Fenilo	460	$2CF_3COOH$
123		4-F-Fenilo	464	$2CF_3COOH$
124		2,6-di-F-Fenilo	482	$2CF_3COOH$
125		4-Me-Fenilo	430	$2CF_3COOH$
126		4-F-Fenilo	434	$2CF_3COOH$
127		2,6-di-F-Fenilo	452	$2CF_3COOH$

Tabla 2

Ejemplo	$-NR^{5a}R^{6a}$	$-R^3$	EIMS (M+1)	HA
128		4-Me-Fenilo	437	$2CF_3COOH$

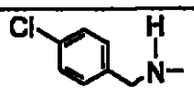
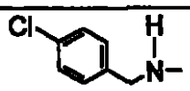
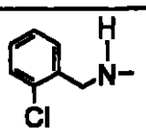
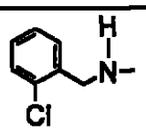
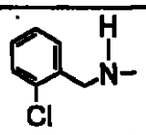
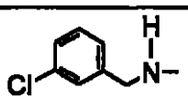
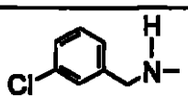
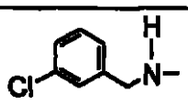
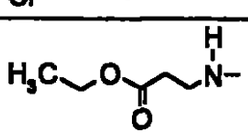
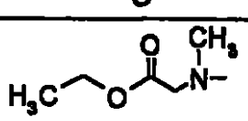
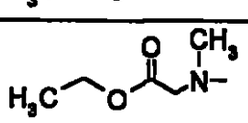
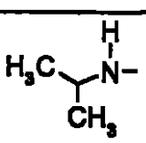
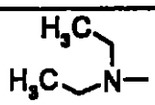
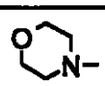
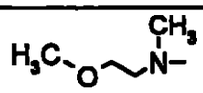
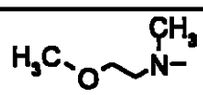
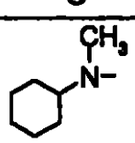
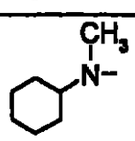
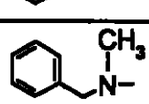
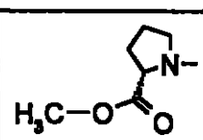
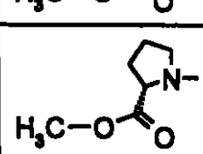
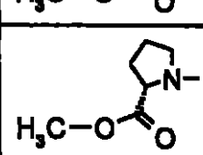
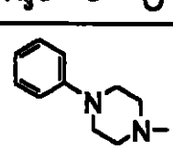
129		4-F-Fenilo	440	$2CF_3COOH$
130		2,6-di-F-Fenilo	458	$2CF_3COOH$
131		4-Me-Fenilo	437	$2CF_3COOH$
132		4-F-Fenilo	440	$2CF_3COOH$
133		2,6-di-F-Fenilo	458	$2CF_3COOH$
134		4-Me-Fenilo	437	$2CF_3COOH$
135		4-F-Fenilo	440	$2CF_3COOH$
136		2,6-di-F-Fenilo	458	$2CF_3COOH$
137		4-Me-Fenilo	412	$2CF_3COOH$
138		4-Me-Fenilo	412	$2CF_3COOH$
139		2,6-di-F-Fenilo	434	$2CF_3COOH$
140		4-Me-Fenilo	354	$2CF_3COOH$
141		4-Me-Fenilo	366	$2CF_3COOH$
142		4-F-Fenilo	370	$2CF_3COOH$
143		2,6-di-F-Fenilo	388	$2CF_3COOH$

Tabla 3

Ejemplo	$-NR^{5a}R^{6a}$	$-R^3$	EIMS (M+1)	HA
144		4-Me-Fenilo	368	$2CF_3COOH$
145		4-Me-Fenilo	382	$2CF_3COOH$
146		4-F-Fenilo	386	$2CF_3COOH$
147		2,6-di-F-Fenilo	404	$2CF_3COOH$
148		4-Me-Fenilo	384	$2CF_3COOH$
149		2,6-di-F-Fenilo	406	$2CF_3COOH$
150		4-Me-Fenilo	408	$2CF_3COOH$
151		2,6-di-F-Fenilo	430	$2CF_3COOH$
152		4-Me-Fenilo	416	$2CF_3COOH$
153		4-Me-Fenilo	424	$2CF_3COOH$
154		4-F-Fenilo	428	$2CF_3COOH$
155		2,6-di-F-Fenilo	446	$2CF_3COOH$
156		4-Me-Fenilo	457	$3CF_3COOH$

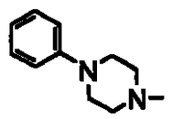
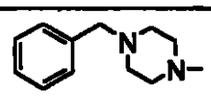
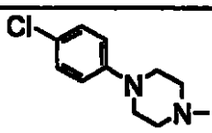
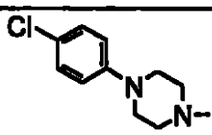
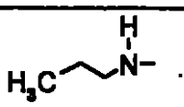
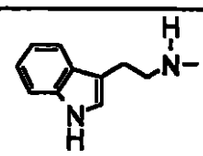
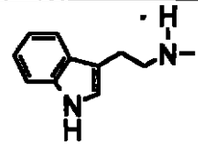
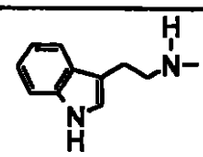
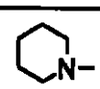
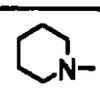
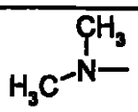
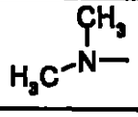
157		4-F-Fenilo	461	$3CF_3COOH$
158		4-Me-Fenilo	471	$3CF_3COOH$

Tabla 4

Ejemplo	$-NR^{5a}R^{6a}$	$-R^3$	EIMS (M+1)	HA
159		4-Me-Fenilo	492	$3CF_3COOH$
160		4-F-Fenilo	496	$3CF_3COOH$
161		4-Me-Fenilo	354	$2CF_3COOH$
162		4-Me-Fenilo	455	
163		4-F-Fenilo	459	
164		2,6-di-F-Fenilo	477	
165		4-F-Fenilo	384	$2CF_3COOH$
166		2,6-di-F-Fenilo	402	$2CF_3COOH$
167		4-F-Fenilo	344	$2CF_3COOH$
168		2,6-di-F-Fenilo	362	$2CF_3COOH$

Ejemplo 169

Dihidrocloruro de 4-(metoxicarbonil)bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) A una solución (20 mL) de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (2,00 g; 4,85 mmol) en N,N-dimetilformamida fue agregado metil 4-(bromometil)benzoato (1,22 g; 5,33 mmol) y carbonato de potasio (1,01 g; 7,28 mmol) y la mezcla fue agitada a la temperatura ambiente por 14 hrs. La mezcla de reacción fue diluida con acetato de etilo (100 mL) y fue lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar 4-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2.50 g, rendimiento 92%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,14-2,25 (1H; m); 2,35 (3H; s); 2,54 (3H; s); 2,78 (2H; d; J = 7,2 Hz); 3,93 (3H; s); 4,12 (2H; d; J = 7,0 Hz); 4,21 (1H; brs); 4,98 (2H; s); 7,01 (2H; d; J = 7,9 Hz); 7,07-7,12 (4H; m), 7,93 (2H; d; J = 8,3 Hz).

2) Dihidrocloruro de 4-(Metoxicarbonil)bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

(427 mg, rendimiento 90%) fue obtenido como polvo blanco de 4-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,50 g; 0,892 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6;8 Hz); 2,20 (1H; m); 2,34 (3H; s); 2,85 (2H; d; J = 6,6 Hz); 3,80 (2H; d; J = 5,3 Hz); 3,87 (3H; s); 5,07 (2H; s); 7,13-7,16 (4H; m); 7,20 (2H; d; J = 7,9 Hz); 7,87 (2H; d; J = 8,3 Hz); 8,22 (3H; brs).

Ejemplo 170

Dihidrocloruro de ácido 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]benzoico

1) El ácido 4-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]benzoico (340 mg, rendimiento 32%) fue obtenido como un aceite incoloro de 4-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,10 g; 1,96 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,16-2,27 (1H; m); 2,35 (3H; s); 2,55 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 4,12 (2H; s); 4,22 (1H; brs); 5,00 (2H; s); 7,02 (2H; d; J = 7,7 Hz); 7,06-7,14 (4H; m); 7,99 (2H; d; J = 8,3

Hz).

2) El dihidrocloruro de ácido 4-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]benzoico (326 mg, rendimiento 93%) fue obtenido como polvo blanco de ácido 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]benzoico (370 mg; 0,677 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,95 (6H; d; J = 6,6 Hz); 2,17-2,27 (1H; m); 2,34 (3H; s); 2,80 (2H; d; J = 7,5 Hz); 3,80 (2H; d; J = 5,8 Hz); 5,06 (2H; s); 7,10-7,14 (4H; m); 7,20 (2H; d; J = 8,1 Hz); 8,10 (3H; brs).

Ejemplo 171

Dihidrocloruro de 2-amino-2-tioxoetil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) A una solución (50 mL) de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (3,00 g; 7,27 mmol) en N,N-dimetilformamida se agregaron los bromoacetonitrilo (0,66 mL; 9,45 mmol) y carbonato de potasio (1,51 g; 10,9 mmol) y la mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue diluida con acetato de etilo (100 mL) y lavó con la solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue

evaporado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar cianometil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2,78 g; rendimiento 85%) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,19-2,28 (1H; m); 2,39 (3H; s); 2,56 (3H; s); 2,80 (2H; d; J = 7,2 Hz); 4,17 (2H; d; J = 4,9 Hz); 4,24 (1H; brs); 4,50 (2H; s); 7,05 (2H; d; J = 8,1 Hz); 7,24 (2H; d; J = 7,9 Hz).

2) El ácido sulfhídrico fuee soplado en una solución (25 mL) de cianometil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2,78 g; 6,16 mmol) y trietilamina (0,94 mL; 6;77 mmol) en N,N-dimetilformamida por 1 hr. El solvente fue evaporado bajo presión reducida y el residuo fue diluído con acetato de etilo (100 mL). La solución fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el sólido amarillo obtenido fue lavado con diisopropil éter para dar 2-amino-2-tioxóetil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2,81 g; rendimiento 94%) como un sólido castaño amarillento.

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,19-2,28 (1H; m); 2,40 (3H; s); 2,56 (3H; s); 2,79 (2H; d; J =

7,4 Hz); 4,14 (2H; d; J = 4,5 Hz); 4,22 (1H; brs); 4,80 (2H; s); 6,21 (1H; brs); 6,98 (1H; brs); 7,13 (2H; d; J = 7,9 Hz); 7,27 (2H; d; J = 7,5 Hz).

3) Dihidrocloruro de 2-amino-2-tioxoetil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (133 mg, rendimiento 70%) fue obtenido como un sólido amarillo de 2-amino-2-tioxoetil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (200 mg; 0,412 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,16-2,27 (1H; m); 2,37 (3H; s); 2,58 (3H; s); 2,83 (2H; d; J = 6,2 Hz); 3,83 (2H; d; J = 5,7 Hz); 4,45 (2H; s); 7,21 (2H; d; J = 7,7 Hz); 7,29 (2H; d; J = 7,9 Hz); 8,16 (3H; brs); 8,98 (1H; brs); 9,85 (1H; brs).

Ejemplo 172

Dihidrocloruro de [4-(etoxicarbonil)-1,3-tiazol-2-il]metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) A una solución mezcla de dihidrocloruro de 2-amino-2-tioxoetil .5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2,02 g; 4,41 mmol) en tetrahidrofurano (30 mL) carbonato hidrógeno de sodio acuoso saturado (10 mL) fue agregado cloroformato de bencilo (903 mg; 5,30 mmol) y la mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue diluida con acetato de etilo (100 mL) y fue lavada con solución salina saturada. La capa orgánica

fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar 2-amino-2-tioxoetil 5-({[(benciloxi)carbonil]amino}metil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2.00 g; rendimiento 87%) como un sólido amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 2,16-2,25 (1H; m); 2,39 (3H; s); 2,56 (3H; s); 2,81 (2H; d; J = 7,4 Hz); 4,22 (2H; d; J = 5,1 Hz); 4;43 (1H; brs); 4;79 (2H; s); 5;04 (2H; s); 6;23 (1H; brs); 6;97 (1H; brs); 7;11 (2H; d; J = 8;1 Hz); 7,24 (2H; d; J = 7,9 Hz); 7,29-7,36 (5H; m).

2) Una solución (70 mL) de 2-amino-2-tioxoetil 5-({[(benciloxi)carbonil]amino}metil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2,00 g; 3,85 mmol) y bromopiruvato de etilo (1,08 g; 5,00 mmol) en etanol fue calentada bajo reflujo por 1 hr. La mezcla de reacción fue diluída con acetato de etilo (200 mL) y lavada con carbonato hidrógeno de sodio acuoso saturado. La capa orgánica fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar [4-(etoxicarbonil)-1,3-tiazol-2-il]metil 5-({[(benciloxi)carbonil]amino}metil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2,37 g; rendimiento 100%) como un

aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,41 (3H; t; J = 7,2 Hz); 2,10-2,26 (1H; m); 2,32 (3H; s); 2,56 (3H; s); 2,82 (2H; d; J = 7,2 Hz); 4,21 (2H; d; J = 5,3 Hz); 4,44 (2H; q; J = 7,0 Hz); 5,03 (3H; s); 5,22 (2H; s); 7,00 (2H; d; J = 8,1 Hz), 7,07 (2H; d; J = 7,9 Hz); 7,22-7,38 (5H; m); 8,15 (1H; s).

3) [4-(Etoxicarbonil)-1,3-tiazol-2-il]metil 5-({[(benciloxi)carbonil]amino}metil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2,37 g; 3,85 mmol) fue disuelto en solución 30% ácido bromhídrico ácido acético (30 mL) y la mezcla fue agitada a la temperatura ambiente por 30 min. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue diselto agregando carbonato hidrógeno de sodio acuoso saturado (30 mL) y tetrahidrofurano (50 mL). Fue agregado bicarbonato de di-terc-butilo (1,02 g; 4,66 mmol) y la mezcla fue agitada a la temperatura ambiente por 15 hrs. La mezcla de reacción fue diluída con acetato de etilo (200 mL) y lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar [4-(etoxicarbonil)-1,3-tiazol-2-il]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,72 g; rendimiento 78%) como un

aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 1,42 (3H; t; J = 7,2 Hz); 2,17-2,27 (1H; m); 2,33 (3H; s); 2,56 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 4,11-4,16 (2H; m); 4,24 (1H; brs); 4,44 (2H; q; J = 7,2 Hz); 5,22 (2H; s); 7,02 (2H; d, J = 8,1 Hz); 7,10 (2H; d, J = 7,9 Hz); 8,16 (1H, s).

4) El dihidrocloruro de [4-(Etoxicarbonil)-1,3-tiazol-2-il]metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (322 mg, rendimiento 90%) fue obtenido como polvo blanco de [4-(etoxicarbonil)-1,3-tiazol-2-il]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (373 mg; 0,643 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 1,32 (3H; t; J = 7,2 Hz); 2,18-2,27 (1H; m); 2,29 (3H; s); 2,55 (3H; s); 2,80-2,92 (2H; m); 3,79 (2H; d; J = 5,3 Hz); 4,32 (2H; q; J = 7,1 Hz); 5,30 (2H; s); 7,12 (4H; s); 8,25 (3H; brs); 8,56 (1H; s).

Ejemplo 173

Dihidrocloruro de ácido 2-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-1,3-tiazol-4-carboxílico

1) El ácido 2-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-

il]carbonil}oxi)metil]-1,3-tiazol-4-carboxílico (1,21 g; rendimiento 95%) fue obtenido como un aceite incoloro de [4-(etoxicarbonil)-1,3-tiazol-2-il]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,34 g; 2,30 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,4 Hz); 1,38 (9H; s); 2,16-2,28 (1H; m); 2,33 (3H; s); 2,61 (3H; brs); 2,85 (2H; brs); 4,11-4,19 (2H; m); 4,23 (1H; brs); 5,22 (2H; s); 7,02 (2H; d; J = 7,9 Hz); 7,10 (2H; d; J = 7,4 Hz); 8,24 (1H; s).

2) El dihidrocloruro de ácido 2-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-1,3-tiazol-4-carboxílico (362 mg, rendimiento 83%) fue obtenido como polvo amarillo pálido del ácido 2-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-1,3-tiazol-4-carboxílico (460 mg; 0,831 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,16-2,27 (1H; m); 2,30 (3H; s); 2,53 (3H; s); 2,85 (2H; d; J = 7,0 Hz); 3,80 (2H; d; J = 5,1 Hz); 5,29 (2H; s); 7,12 (4H; s); 8,21 (3H; brs); 8,48 (1H; s).

Ejemplo 174

Dihidrocloruro de [4-(aminocarbonil)-1,3-tiazol-2-il]metil 5-

(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) [4-(Aminocarbonil)-1,3-tiazol-2-il]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (420 mg, rendimiento 70%) fue obtenido como un aceite incoloro del ácido 2-[([[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-1,3-tiazol-4-carboxílico (602 mg, 1.09 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,18-2,27 (1H; m); 2,33 (3H; s); 2,57 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 4,10-4,16 (2H; m); 4,22 (1H; brs); 5,17 (2H; s); 5,64 (1H; brs); 7,01 (2H; d; J = 7,9 Hz); 7,09 (2H; d; J = 7,9 Hz); 8,13 (1H; s).

2) Dihidrocloruro de [4-(Aminocarbonil)-1,3-tiazol-2-il]metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (208 mg, rendimiento 48%) fue obtenido como polvo blanco de [4-(aminocarbonil)-1,3-tiazol-2-il]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (460 mg; 0,832 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,18-2,27 (1H; m); 2,30 (3H; s); 2,53 (3H; s); 2,79-2,89 (2H; m); 3,79 (2H; d; J = 5,5 Hz); 5,28 (2H; s); 7,12 (4H; s); 7,62 (1H; brs);

7,66 (1H; brs); 8,22 (3H; brs); 8,48 (1H; s).

Ejemplo 175

Dihidrocloruro de [(2,2-dimetilpropanoil)oxi]metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) A una solución (20 mL) del ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,50 g; 3,37 mmol) en N,N-dimetilformamida se agregaron los pivalato de clorometilo (0,59 mL; 4,04 mmol) y carbonato de potasio (0,93 g; 6,72 mmol) y la mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y lavada con la solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar [(2,2-dimetilpropanoil)oxi]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,68 g; rendimiento 95%) como un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,16 (9H; s); 1,39 (9H; s); 2,14-2,29 (1H; m); 2,38 (3H; s); 2,54 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 4,13 (2H; d; J = 4,9 Hz); 4,21 (1H; brs); 5,57 (2H; s); 7,06 (2H; d; J = 8,1 Hz); 7,20 (2H; d; J = 7,9 Hz).

2) Dihidrocloruro de [(2,2-dimetilpropanoil)oxi]metil 5-

(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,58 g; rendimiento 99%) fue obtenido como un sólido blanco de [(2,2-dimetilpropanoil)oxi]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,68 g; 3,19 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 1,09 (9H; s); 2,17-2,29 (1H; m); 2,37 (3H; s); 2,49 (3H; s); 2,84 (2H; d; J = 7,0 Hz); 3,78 (2H; d; J = 5,5 Hz); 5,61 (2H; s); 7,19 (2H; d; J = 8,1 Hz); 7,28 (2H; d; J = 8,1 Hz); 8,20 (3H; brs).

Ejemplo 176

dihidrocloruro de (5-metil-2-oxo-1,3-dioxol-4-il)metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) A una solución (20 mL) de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,50 g; 3,37 mmol) en N,N-dimetilformamida fue agregado 4-(clorometil)-5-metil-1,3-dioxol-2-ona (0,60 g; 4,04 mmol) y carbonato de potasio (0,93 g; 6,72 mmol) y la mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y la mezcla fue lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar (5-metil-

2-oxo-1,3-dioxol-4-il)metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,50 g; rendimiento 85%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,38 (9H; s); 1,97 (3H; s); 2,16-2,26 (1H; m); 2,40 (3H; s); 2,54 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 4,09 (2H; s); 4,74 (2H; s); 7,10 (2H; d; J = 7,9 Hz); 7,17 (2H; d; J = 7,9 Hz).

2) Dihidrocloruro de (5-metil-2-oxo-1,3-dioxol-4-il)metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,21 g; rendimiento 85%) fue obtenido como polvo blanco de (5-metil-2-oxo-1,3-dioxol-4-il)metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,50 g; 2,86 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 1,97 (3H; s); 2,17-2,28 (1H; m); 2,35 (3H; s); 2,82 (2H; d; J = 7,0 Hz); 3,79 (2H; d; J = 5,5 Hz); 4,93 (2H; s); 7,12 (2H; d; J = 8,1 Hz); 7,20 (2H; d; J = 7,9 Hz); 8,15 (3H; brs).

Ejemplo 177

Dihidrocloruro de 3-oxo-1,3-dihidro-2-benzofuran-1-il 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) A una solución (30 mL) de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-

metilfenil)nicotínico (1,50 g; 3,37 mmol) en N,N-dimetilformamida fue agregado 3-cloro-2-benzofuran-1(3H)-ona (0,86 g; 4,04 mmol) y carbonato de potasio (0,93 g; 6,72 mmol) y la mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y la mezcla fue lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar 3-oxo-1,3-dihidro-2-benzofuran-1-il 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,83 g; rendimiento 99%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,16-2,25 (1H; m); 2,42 (3H; s); 2,63 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 4,12 (2H; s); 6,98-7,08 (3H; m); 7,17 (2H; d; J = 7,9 Hz); 7,24 (1H; s); 7,59-7,64 (2H; m); 7,83-7,88 (1H; m).

2) Dihidrocloruro de 3-Oxo-1,3-dihidro-2-benzofuran-1-il 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

fue obtenido como polvo blanco de 3-oxo-1,3-dihidro-2-benzofuran-1-il 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,83 g; 3,36 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,95 (6H; d; J = 6,6 Hz); 2,15-2,28 (1H;

m); 2,38 (3H; s); 2,59 (3H; s); 2,81 (2H; d; J = 7,2 Hz); 3,79 (2H; d; J = 5,7 Hz); 7,07-7,15 (3H; m); 7,25-7,32 (2H; m); 7,40 (1H; s); 7,73-7,75 (1H; m); 7,79-7,84 (1H; m); 7,89 (1H; d; J = 7,5 Hz); 8,12 (3H; brs).

Ejemplo 178

Dihidrocloruro de (2E)-2-(3-oxo-2-benzofuran-1(3H)-iliden)etil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) A una solución (10 mL) de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (380 mg; 0,853 mmol) en N,N-dimetilformamida fue agregado (3E)-3-(2-cloroetiliden)-2-benzofuran-1(3H)-ona (170 mg; 0,711 mmol) y carbonato de potasio (147 mg; 1,07 mmol) y la mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue diluida con acetato de etilo (100 mL) y la mezcla fue lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar (2E)-2-(3-oxo-2-benzofuran-1(3H)-iliden)etil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (270 mg, rendimiento 55%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,16-

2,26 (4H; m); 2,58 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 4,12 (2H; s); 4,21 (1H; brs); 4,85 (2H; d; J = 7,4 Hz); 5,25 (1H; t; J = 7,4 Hz); 7,07 (2H; d; J = 8,3 Hz); 7,12 (2H; d; J = 8,1 Hz); 7,55-7,64 (2H; m); 7,72-7,78 (1H; m); 7,92-7,95 (1H; m).

2) Dihidrocloruro de (2E)-2-(3-Oxo-2-benzofuran-1(3H)-iliden)etil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (204 mg, rendimiento 79%) fue obtenido como polvo blanco de (2E)-2-(3-oxo-2-benzofuran-1(3H)-iliden)etil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (270 mg; 0,473 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,95 (6H; d; J = 6,6 Hz); 2,07 (3H; s); 2,18-2,29 (1H; m); 2,79 (2H; d; J = 6,6 Hz); 3,78 (2H; d; J = 7,4 Hz); 4,81 (2H; d; J = 7,5 Hz); 5,68 (1H; t; J = 7,5 Hz); 7,14 (4H; s); 7,71-7,77 (1H; m); 7,90-8,00 (3H; m); 8,06 (3H; brs).

Ejemplo 179

Bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

A una solución (30 mL) de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (3,00 g; 6,73 mmol) en N,N-dimetilformamida fue agregado el bromuro del bencilo (0,80 mL; 6,73 mmol) y carbonato de potasio (1,85 g; 13,4 mmol) y

la mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue diluida con acetato de etilo (200 mL) y la mezcla fue lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo obtenido fue disuelto en el ácido trifluoracético (50 mL) y la mezcla fue agitada a la temperatura ambiente por 3 hrs. El ácido trifluoracético fue evaporado bajo presión reducida, y el residuo fue neutralizado con carbonato hidrógeno de sodio acuoso saturado. La mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2,70 g; rendimiento 99%) como un sólido amarillo.

^{1}H-RMN ($CDCl_3$) δ:0,91 (6H; d; J = 6,6 Hz); 2,07-2,18 (1H; m); 2,34 (3H; s); 2,51 (3H; s); 2,72 (2H; d; J = 7,4 Hz); 3,84 (2H; s); 4,94 (2H; s); 7,02-7,12 (6H; m); 7,24-7,31 (3H; m).

Ejemplo 180

Dihidrocloruro de 2-oxo-1,3-dioxolan-4-il 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) A una solución (30 mL) de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-

metilfenil)nicotínico (1,50 g; 3,37 mmol) en N,N-dimetilformamida fue agregado 4-cloro-1,3-dioxolan-2-ona (0,55 g; 4,04 mmol) y carbonato de potasio (0,70 g; 5,05 mmol) y la mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y la mezcla fue lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar 2-oxo-1,3-dioxolan-4-il 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,39 g; rendimiento 83%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,19-2,28 (1H; m); 2,41 (3H; s); 2,60 (3H; s); 2,81 (2H; d; J = 7,4 Hz); 3,67 (1H; dd; J = 10,2; 1,5 Hz); 4,16 (2H; d; J = 4;9 Hz); 4;22 (1H; brs); 4;31 (1H; dd; J = 10;0; 5;7 Hz); 4,63-4,82 (1H; m); 6,41-6,46 (1H; m); 7,01-7,10 (2H; m); 7,19-7,26 (2H; m).

2) Dihidrocloruro de 2-Oxo-1,3-dioxolan-4-il 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,31 g; rendimiento 99%) fue obtenido como polvo blanco de 2-oxo-1,3-dioxolan-4-il 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,39 g; 2,79 mmol) según un método

similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,18-2,28 (1H; m); 2,36 (3H; s); 2,55 (3H; s); 2,85 (2H; d; J = 7,0 Hz); 3,83 (2H; d; J = 5,7 Hz); 4,04 (1H; dd; J = 10,2; 1,7 Hz); 4,59 (1H; dd; J = 10,1; 5,7 Hz); 6,59 (1H; dd; J = 5,4 Hz); 7,14-7,20 (2H, m); 7,24-7,29 (2H; m); 8,23 (3H; brs).

Ejemplo 181

Dihidrocloruro de ácido 5-(aminometil)-4-(4-hidroxifenil)-6-isobutil-2-metilnicotínico

1) Terc-butil 4-[4-(benciloxi)fenil]-5-ciano-6-isobutil-2-metil-1,4-dihidropiridin-3-carboxilato (21,4 g; rendimiento 77%) fue obtenido como sólido rosa pálido de 4-(benciloxi)benzaldehído (12,8 g; 60,4 mmol) según un método similar al método del Ejemplo 1-2).

^{1}H-RMN ($CDCl_3$) δ:0,94 (3H; d; J = 6,6 Hz); 0,99 (3H; d; J = 6,6 Hz); 1,28 (9H; s); 1,80-1,96 (1H; m); 2,14-2,29 (2H; m); 2,32 (3H; s); 4,51 (1H; s); 5,03 (2H; s); 5,49 (1H; s); 6,90 (2H; d; J = 8,7 Hz); 7,15 (2H; d; J = 8,7 Hz); 7,29-7,46 (5H; m).

2) Terc-butil 4-[4-(benciloxi)fenil]-5-ciano-6-isobutil-2-metilnicotinato (2,18 g; rendimiento 94%) fue obtenido como un sólido amarillo de terc-butil 4-[4-(benciloxi)fenil]-5-ciano-6-isobutil-2-metil-1,4-dihidropiridin-3-carboxilato (2,33 g; 5,08 mmol) según un método similar al método del

Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,6 Hz); 1,25 (9H; s); 2,17-2,33 (1H; m); 2,63 (3H; s); 2,93 (2H; d; J = 7,4 Hz); 5,12 (2H; s); 7,06 (2H; d; J = 8,9 Hz); 7,31 (2H; d; J = 8,9 Hz); 7,39-7,49 (5H; m).

3) Terc-butil 5-(aminometil)-4-(4-hidroxifenil)-6-isobutil-2-metilnicotinato fue obtenido como un producto en bruto de terc-butil 4-[4-(benciloxi)fenil]-5-ciano-6-isobutil-2-metilnicotinato (2,13 g; 4,67 mmol) según un método similar al método del Ejemplo 1-4). El terc-butil 5-{[(terc-butoxicarbonil)amino]metil}-4-(4-hidroxifenil)-6-isobutil-2-metilnicotinato (1,35 g; rendimiento 61%) fue obtenido como un sólido amarillo pálido del producto en bruto según un método similar al método del Ejemplo 2-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,22 (9H; s); 1,40 (9H; s); 2,12-2,27 (1H; m); 2,55 (3H; s); 2,76 (2H; d; J = 7,2 Hz); 4,14 (2H; d; J = 4,9 Hz); 4,25 (1H; brs); 5,50 (1H; brs); 6,85 (2H; d; J = 8,5 Hz); 7,07 (2H; d; J = 8,5 Hz).

4) El terc-butil 5-{[(terc-butoxicarbonil)amino]metil}-4-(4-hidroxifenil)-6-isobutil-2-metilnicotinato (316 mg; 0,671 mmol) y anisol (218 mg, 2.01 mmol) fue disuelto en ácido trifluoracético (5 mL) y la mezcla fue agitada a la temperatura ambiente por 5 hrs. El ácido trifluoracético fue evaporado bajo presión reducida y fue agregada solución 4N

cloruro de hidrógeno 1,4-dioxano (20 mL) al residuo. La mezcla fue agitada a la temperatura ambiente por 30 min. El solvente fue evaporado bajo presión reducida y el sólido amarillo obtenido fue lavado con diisopropil éter para dar dihidrocloruro de ácido 5-(aminometil)-4-(4-hidroxifenil)-6-isobutil-2-metilnicotínico (259 mg, rendimiento 99%) como un polvo amarillo.

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,14-2,27 (1H; m); 2,59 (3H; s); 2,92 (2H; d; J = 5,7 Hz); 3,86 (2H; d; J = 4,9 Hz); 6,87 (2H; d; J = 8,5 Hz); 7,14 (2H; d; J = 8,3 Hz); 8,26 (3H; brs).

Ejemplo 182

Dihidrocloruro de ácido 5-(aminometil)-6-isobutil-4-(4-metoxifenil)-2-metilnicotínico

1) A una solución (20 mL) de terc-butil 5-{[(terc-butoxicarbonil)amino]metil}-4-(4-hidroxifenil)-6-isobutil-2-metilnicotinato (620 mg; 1,32 mmol) y carbonato de potasio (365 mg; 2,64 mmol) en N,N-dimetilformamida fue agregado iodometano (374 mg; 2,64 mmol) y la mezcla fue agitada a la temperatura ambiente por 30 min. La mezcla de reacción fue diluida con acetato de etilo (100 mL) y la mezcla fue lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar terc-

butil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metoxifenil)-2-metilnicotinato (520 mg, rendimiento 81%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,21 (9H; s); 1,39 (9H; s); 2,13-2,26 (1H; m); 2,55 (3H; s); 2,76 (2H; d; J = 7,4 Hz); 3,84 (3H; s); 4,12 (2H; s); 4,22 (1H; brs); 6,94 (2H; d; J = 8,7 Hz); 7,12 (2H; d; J = 8,7 Hz).

2) Dihidrocloruro de ácido 5-(Aminometil)-6-isobutil-4-(4-metoxifenil)-2-metilnicotínico (429 mg, rendimiento 99%) fue obtenido como polvo amarillo de terc-butil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metoxifenil)-2-metilnicotinato (520 mg; 1,07 mmol) según un método similar al método del Ejemplo 181-4).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,16-2,27 (1H; m); 2,54 (3H; s); 2,85 (2H; d; J = 6,6 Hz); 3,57(3H; s); 3,84 (2H; s); 7,05 (2H; d; J = 8,7 Hz); 7,26 (2H; d; J = 8,7 Hz); 8,17 (3H; brs).

Ejemplo 183

Dihidrocloruro de metil 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoato

1) Una mezcla de terc-butilo {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,00 g; 2,51 mmol), trietilamina (0,7 mL; 5,02 mmol) y tetrahidrofurano (20 mL) fue enfriada a 0°C y fue agregado

cloruro de metansulfonilo (432 mg; 3,77 mmol) por gotas. Después de agitar a temperatura ambiente por 30 min., la mezcla de reacción fue vertida en carbonato de hidrógeno de sodio acuoso saturado, y la mezcla se extrajo con acetato de etilo. El extracto fue secado sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida para dar metansulfonato [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilo como un producto en bruto. El producto en bruto fue disuelto en N,N-dimetilformamida (15 mL), y carbonato de potasio (520 mg; 3,77 mmol) fue agregado y metil 4-mercaptobenzoato (422 mg, 2,51 mmol). La mezcla fue agitada con calentamiento a 50°C por 1 hr. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y la mezcla fue lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar metil 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoato (1,01 g; rendimiento 73%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,16-2,25 (1H; m); 2,37 (3H; s); 2,65 (3H; s); 2,75 (2H; d; J = 7,4 Hz); 3,86 (2H; s); 3,89 (3H; s); 4,04 (2H; d; J = 5,1

Hz); 4,20 (1H; brs); 7,04 (2H; d; J = 7,9 Hz); 7,09 (2H; d; J = 8,7 Hz); 7,19 (2H; d; J = 7,7 Hz); 7,85 (2H; d; J = 8,7 Hz).

2) Dihidrocloruro de metil 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoato (138 mg, rendimiento 73%) fue obtenido como polvo amarillo pálido de metil 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoato (200 mg; 0,365 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,12-2,23 (1H; m); 2,35 (3H; s); 2,81 (3H; s); 3,64 (2H; brs); 3,75 (2H; d; J = 5,7 Hz); 3,83 (3H; s); 4,01 (2H; s); 7,24-7,33 (6H; m); 7,82 (2H; d; J = 8,7 Hz); 8,30 (3H; brs).

Ejemplo 184

Dihidrocloruro de ácido 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoico

1) El ácido 4-({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoico (0,97 g; rendimiento 72%) fue obtenido como un sólido blanco de metil 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoato (1,37 g; 2,51 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:1,07 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,23-

2,35 (1H; m); 2,42 (3H; s); 3,08 (3H; s); 3,30-3,40 (2H; m); 3,90 (2H; s); 4,12-4,18 (2H; m); 4,30 (1H; brs); 7,05 (2H; d; J = 7,9 Hz); 7,13 (2H; d; J = 8,5 Hz); 7,23-7,31 (2H; m); 7.93 (2H, d, J = 8,5 Hz).

2) Dihidrocloruro de ácido 4-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoico (198 mg, rendimiento 77%) fue obtenido como polvo blanco de ácido 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoico (0,27 g; 0,505 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,13-2,23 (1H; m); 2,36 (3H; s); 2,81 (3H; s); 3,05 (2H; brs); 3,71-3,80 (2H; m); 4,01 (2H; s); 7,23-7,27 (4H; m); 7,32 (2H; d; J = 8,1 Hz); 7,80 (2H; d; J = 8,3 Hz); 8,32 (3H; brs).

Ejemplo 185

Dihidrocloruro de metil 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}sulfonil)benzoato

1) Metil 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}sulfonil)benzoato (410 mg, rendimiento 84%) fue obtenido como un aceite incoloro de metil 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoato (0,46 g; 0,838 mmol) según un método similar al método del Ejemplo 91-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,7 Hz); 1,38 (9H; s); 2,17-2,26 (1H; m); 2,41 (3H; s); 2,64 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,98 (3H; s); 4,00 (2H; d; J = 5,3 Hz); 4,18 (1H; brs); 4,32 (2H; s); 6,87 (2H; d; J = 7,7 Hz); 7,17 (2H; d; J = 7,7 Hz); 7,56 (2H; d; J = 8,5 Hz); 8,08 (2H; d; J = 8,5 Hz).

2) Dihidrocloruro de metil 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}sulfonil)benzoato (352 mg, rendimiento 90%) fue obtenido como polvo amarillo pálido de metil 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}sulfonil)benzoato (410 mg; 0,706 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,17-2,27 (1H; m); 2,38 (3H; s); 2,78 (3H; s); 3,00 (2H; brs); 3,66-3,74 (2H; m); 3,93 (3H; s); 4,61 (2H; brs); 7,05 (2H; d; J = 7,9 Hz); 7,23 (2H; d; J = 7,9 Hz); 7,66 (2H; d; J = 8,3 Hz); 8,09 (2H, d, J = 8.7 Hz), 8,30 (3H; brs).

Ejemplo 186

Dihidrocloruro de ácido 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}sulfonil)benzoico

1) El ácido 4-({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}sulfonil)benzoico (300 mg, rendimiento 93%) fue

obtenido como un aceite incoloro de metil 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}sulfonil)benzoato (330 mg, 0,568 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,14-2,22 (1H; m); 2,34 (3H; s); 2,43 (3H; s); 2,86 (2H; d; J = 7,4 Hz); 4,06 (2H; d; J = 4,5 Hz); 4,28 (1H; brs); 4,35 (2H; s); 6,97 (2H; d; J = 7,9 Hz); 7,23 (2H; d; J = 7,7 Hz); 7,60 (2H, d, J = 8,1 Hz); 8,17 (2H; d; J = 8,1 Hz).

2) Dihidrocloruro de ácido 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}sulfonil)benzoico (279 mg, rendimiento 97%) fue obtenido como polvo blanco de ácido 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}sulfonil)benzoico (300 mg; 0,530 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,17-2,24 (1H; m); 2,38 (3H; s); 2,76 (3H; brs); 2,95 (2H; brs); 3,70 (2H; brs); 7,05 (2H; d; J = 7,9 Hz); 7,23 (2H; d; J = 7,9 Hz); 7,62 (2H; d; J = 8,3 Hz); 8,07 (2H; d; J = 8,3 Hz); 8,24 (3H; brs).

Ejemplo 187

Dihidrocloruro de N-{[5-(aminometil)-6-isobutil-2-metil-4-(4-

metilfenil)piridin-3-il]metil}metansulfonamida

1) A una solución (10 mL) de terc-butilo {[5-(aminometil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (200 mg; 0,755 mmol) y trietilamina (0,14 mL; 1,00 mmol) en tetrahidrofurano fue agregado cloruro de metansulfonilo (86 mg, 0,875 mmol) y la mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue diluida con acetato de etilo (100 mL) y fue lavada consecutivamente con carbonato hidrógeno de sodio acuoso saturado y solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el sólido amarillo obtenido fue lavado con diisopropil éter para dar terc-butil [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[(metilsulfonil)amino]metil}piridin-3-il)metil]carbamato (210 mg, rendimiento 87%) como un sólido blanco.

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,16-2,25 (1H; m); 2,42 (3H; s); 2,61 (3H; s); 2,68 (3H; s); 2,76 (2H; d; J = 7,4 Hz); 3,87 (1H; brs); 4,01 (2H; d; J = 5,7 Hz); 4,03 (2H; d; J = 5,3 Hz); 4,18 (1H; brs); 7,03 (2H; d; J = 8,1 Hz); 7,29 (2H; d; J = 7,9 Hz).

2) Dihidrocloruro de N-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}metansulfonamida (126 mg, rendimiento 64%) fue obtenido como polvo blanco de terc-butilo [(2-isobutil-6-metil-4-(4-metilfenil)-5-

{[(metilsulfonil)amino]metil}piridin-3-il)metil]carbamato (210 mg; 0,441 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,12-2,23 (1H; m); 2,41 (3H; s); 2,71 (3H; s); 2,84 (3H; brs); 3,04 (2H; brs); 3,76 (2H; brs); 3,87 (2H; brs); 7,19 (1H; brs); 7,29 (2H; d; J = 7,5 Hz); 7,38 (2H; d; J = 7,7 Hz); 8,28 (3H; brs).

Ejemplo 188

Dihidrocloruro de {[4-(2,4-diclorofenil)-6-(4-fluorofenil)-2-isobutilpiridin-3-il]metil}amina

1). (2E)-3-(2,4-Diclorofenil)-1-(4-fluorofenil)prop-2-en-1-ona (10,3 g; rendimiento 64%) fue obtenido como un sólido amarillo pálido de 4-fluoroacetofenona (6,91 g; 50 mmol) y 2,6-diclorobenzamida (8,75 g; 59 mmol) según un método similar al método del Ejemplo 108-1).

^{1}H-RMN ($CDCl_3$) δ: 7,16-7,23 (2H; m); 7,31 (1H; dd; J = 8,5; 2,1 Hz); 7,42-7,49 (2H; m); 7,68 (2H; d; J = 8,5 Hz); 8,07 (3H; m).

2) El 4-(2,4-Diclorofenil)-6-(4-fluorofenil)-2-isobutilnicotinonitrilo (2,94 g; rendimiento 48%) fue obtenido como un aceite amarillo de (2E)-3-(2,4-diclorofenil)-1-(4-fluorofenil)prop-2-en-1-ona (4,54 g; 15,4 mmol) según un método similar al método del Ejemplo 108-2).

^{1}H-RMN ($CDCl_3$) δ:1,06 (6H; d; J = 6,6 Hz); 2,32-2,45 (1H; m); 3,04 (2H; d; J = 7,2 Hz); 7,09-7,24 (3H; m); 7,33 (1H; d; J = 8,3 Hz); 7,37-7,44 (1H; m); 7,57 (1H; s); 7,59 (1H; d; J = 1,9 Hz); 8,06-8,12 (1H; m).

3) El {[4-(2,4-Diclorofenil)-6-(4-fluorofenil)-2-isobutilpiridin-3-il]metil}amina (780 mg, rendimiento 68%) fue obtenido como un aceite amarillo pálido de 4-(2,4-diclorofenil)-6-(4-fluorofenil)-2-isobutilnicotinonitrilo (1,14 g; 2,85 mmol) según un método similar al método del Ejemplo 23-4). El aceite fue disuelto en solución 4N de cloruro hidrógeno 1,4-dioxano (20 mL) y la mezcla fue agitada a temperatura ambiente por 30 min. El solvente fue evaporado bajo presión reducida y el sólido amarillo pálido obtenido fue lavado con diisopropil éter para dar dihidrocloruro de {[4-(2,4-diclorofenil)-6-(4-fluorofenil)-2-isobutilpiridin-3-il]metil}amina (895 mg, rendimiento 97%) como un polvo amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ:0,97 (3H; d; J = 6,6 Hz); 1,05 (3H; d; J = 6,6 Hz); 2,29-2,38 (1H; m); 2,81-2,99 (2H; m); 3,57-3,64 (1H; m); 4,04-4,16 (1H; m); 7,33 (2H; t; J = 8,8 Hz); 7,59-7,67 (2H; m); 7,73 (1H; s); 7,86 (1H; d; J = 1,9 Hz); 8,21-8,30 (5H, m).

Ejemplo 189

Dihidrocloruro de metil 3-[5-(aminometil)-6-isobutil-4-(4-

metilfenil)piridin-2-il]benzoato

1) (2E)-1-(3-Bromofenil)-3-(4-metilfenil)prop-2-en-1-ona (7.09 g; rendimiento 47%) fue obtenido como polvo amarillo pálido de 3-bromoacetofenona (9,95 g; 50 mmol) según un método similar al método del Ejemplo 108-1).

2) El 6-(3-Bromofenil)-2-isobutil-4-(4-metilfenil)nicotinonitrilo (2,20 g; rendimiento 32%) fue obtenido como un sólido amarillo pálido de (2E)-1-(3-Bromofenil)-3-(4-metilfenil)prop-2-en-1-ona (5,03 g; 16,7 mmol) según un método similar al método del Ejemplo 108-2).

^{1}H-RMN ($CDCl_3$) δ:1,06 (6H; d; J = 6,6 Hz); 2,35-2,42 (1H; m); 2,45 (3H; s); 3,06 (2H; d; J = 7,4 Hz); 7,09-7,16 (3H; m); 7,30-7,40 (4H; m); 7,53-7,55 (1H; m); 7,64 (1H; s).

3) El 6-(3-Bromofenil)-2-isobutil-4-(4-metilfenil)nicotinonitrilo (2,20 g; 5,40 mmol), trietilamina (0,70 mL; 10,0 mmol) y [1,1'- bicloruro de bis(difenilfosfino)ferroceno]paladio(II) (410 mg, 0.500 mmol) fue disuelto en una mezcla de solvente de metanol (10 mL)-N,N-dimetilformamida (30 mL) y la mezcla fue agita bajo atmósfera de monóxido de carbono por 15 hrs. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y la mezcla fue lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel

de silice para dar metil 3-[5-ciano-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato (1,39 g; rendimiento 72%) como un aceite incoloro. Metil 3-[5-(aminometil)-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato (780 mg, rendimiento 58%) fue obtenido como un aceite incoloro de metil 3-[5-ciano-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato (1,30 g; 3,38 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:1,05 (6H; d; J = 6,6 Hz); 2,37-2,48 (4H; m); 2,90 (2H; d; J = 7,2 Hz); 3,84 (2H; s); 3,94 (3H; s); 7,27-7,33 (4H; m); 7,49 (1H; s); 7,54 (1H; t; J = 7,9 Hz); 8,04-8,07 (1H; m); 8,32 (1H; m); 8,61-8,62 (1H; m).

4) El metil 3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato (730 mg, rendimiento 76%) fue obtenido como polvo blanco de metil 3-[5-(aminometil)-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato (0,76 g; 1,96 mmol) según un método similar al método del Ejemplo 2-1).

^{1}H-RMN ($CDCl_3$) δ:1,04 (6H; d; J = 6,6 Hz); 1;43 (9H; s); 2,37-2,46 (4H; m); 2,87 (2H; d; J = 7,2 Hz); 3,94 (3H; s); 4,29-4,35 (2H; m); 4,38 (1H; brs); 7,23 (2H; d; J = 8,3 Hz); 7,28 (2H; d; J = 8,1 Hz); 7,50 (1H; s); 7,54 (1H; t; J = 7,8 Hz); 8,05-8,08 (1H; m); 8,30-8,34 (1H; m); 8,62-8,63 (1H, m).

5) El dihidrocloruro de metil 3-[5-(aminometil)-6-isobutil-

4-(4-metilfenil)piridin-2-il]benzoato (188 mg, rendimiento 99%) fue obtenido como polvo blanco de metil 3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato (200 mg; 0,409 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,04 (6H; d; J = 6,4 Hz); 2,33-2,44 (4H; m); 2,93 (2H; d; J = 7,0 Hz); 3,90 (3H; s); 4,01 (2H; d; J = 5,5 Hz); 7,36 (2H; d; J = 8,1 Hz); 7,41 (2H; d; J = 8,3 Hz); 7,66 (1H; t; J = 7,8 Hz); 7,76 (1H; s); 8,01-8,08 (1H; m); 8,40 (3H; brs); 8,42-8,47 (1H; m); 8,71-8,75 (1H; m).

Ejemplo 190

Dihidrocloruro de ácido 3-[5-(aminometil)-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoico

1) El ácido 3-[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoico (500 mg, rendimiento 98%) fue obtenido como un sólido blanco de metil 3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato (530 mg; 1,08 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:1,05 (6H; d; J = 6,6 Hz); 1;43 (9H; s); 2,35-2,47 (4H; m); 2,92 (2H; brs); 4,31-4,37 (2H; m); 4,42 (1H; brs); 7,22-7,30 (4H; m); 7,52 (1H; s); 7,58 (1H; t; J = 7,5 Hz); 8,12 (1H; d; J = 7,9 Hz); 8,36 (1H; d; J = 7,4 Hz); 8,67 (1H, s).

2) El dihidrocloruro de ácido 3-[5-(Aminometil)-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoico (188 mg, rendimiento 99%) fue obtenido como polvo blanco del ácido 3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoico (200 mg; 0,421 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,03 (6H; d; J = 7,4 Hz); 2,32-2,43 (4H; m); 2,92 (2H; d; J = 7,0 Hz); 4,02 (2H; d; J = 5,3 Hz); 7,36 (2H; d; J = 8,1 Hz); 7,41 (2H; d; J = 8,3 Hz); 7,63 (1H; t; J = 7,8 Hz); 7,74 (1H; s); 8,01-8,04 (1H; m); 8,35 (3H; brs); 8,37-8,41 (1H; m); 8,71-8,72 (1H; m).

Ejemplo 191

Dihidrocloruro de 3-[5-(aminometil)-6-isobutil-4-(4-metilfenil)piridin-2-il]benzamida

1) Terc-butil {[6-[3-(aminocarbonil)fenil]-2-isobutil-4-(4-metilfenil)piridin-3-il]metil}carbamato (160 mg, rendimiento 53%) fue obtenido como un sólido blanco de ácido 3-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoico (300 mg; 0,632 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:1,04 (6H; d; J = 6,6 Hz); 1;43 (9H; s); 2,34-2,48 (4H; m); 2,87 (2H; d; J = 7,2 Hz); 4,32 (2H; d; J = 4,7 Hz); 4,39 (1H; brs); 7,22 (2H; d; J = 8,1 Hz); 7,25-7,29 (2H; m); 7,50 (1H; s); 7,55 (1H; t; J = 7,8 Hz); 7,83-7,87 (1H;

m); 8,21-8,25 (1H; m); 8,45-8,46 (1H; m).

2) Dihidrocloruro de 3-[5-(Aminometil)-6-isobutil-4-(4-metilfenil)piridin-2-il]benzamida (127 mg, rendimiento 84%) fue obtenido como polvo blanco de terc-butil {[6-[3-(aminocarbonil)fenil]-2-isobutil-4-(4-metilfenil)piridin-3-il]metil}carbamato (160 mg; 0,338 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,03 (6H; d; J = 6,6 Hz); 2,34-2,44 (4H; m); 2,93 (2H; d; J = 7,0 Hz); 4,01 (2H; d; J = 5,5 Hz); 7,37 (2H; d; J = 8,1 Hz); 7,42 (2H; d; J = 8,1 Hz); 7,47 (1H; brs); 7,60 (1H; t; J = 7,8 Hz); 7,81 (1H; s); 7,96 (1H; d; J = 7,7 Hz); 8,14 (1H; brs); 8,33-8,44 (4H; m); 8,58 (1H, s).

Ejemplo 192

Dihidrocloruro de metil 2-[5-(aminometil)-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato

1) (2E)-1-(2-Bromofenil)-3-(4-metilfenil)prop-2-en-1-ona (8,86 g; rendimiento 44%) fue obtenido como polvo amarillo pálido de 2-bromoacetofenona (9,95 g; 50 mmol) según un método similar al método del Ejemplo 108-1).

2) El 6-(2-Bromofenil)-2-isobutil-4-(4-metilfenil)nicotinonitrilo (3,58 g; rendimiento 53%) fue obtenido como un sólido amarillo pálido de (2E)-1-(2-Bromofenil)-3-(4-metilfenil)prop-2-en-1-ona (5,03 g; 16,7 mmol) según un método similar al método del Ejemplo 108-2).

^{1}H-RMN ($CDCl_3$) δ:1,06 (6H; d; J = 6,6 Hz); 2,34-2,44 (4H; m);

3,07 (2H; d; J = 7,4 Hz); 7,27-7,30 (1H; m); 7,32-7,36 (2H; m); 7,41-7,47 (1H; m); 7,53-7,60 (3H; m); 7,71 (1H; m).

3) El metil 2-[5-ciano-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato (1,80 g; rendimiento 76%) fue obtenido como un aceite incoloro de 6-(2-Bromofenil)-2-isobutil-4-(4-metilfenil)nicotinonitrilo (2,50 g; 6,14 mmol) según un método similar al método del Ejemplo 189-3). Es decir, 6-(2-Bromofenil)-2-isobutil-4-(4-metilfenil)nicotinonitrilo, trietilamina (1,7 mL; 12,2 mmol) y bicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio(II) (501 mg; 0,614 mmol) fue disuelto en metanol (7,5 mL) - N,N-dimetilformamida (15 mL) y la mezcla fue agitada bajo atmósfera de monóxido de carbono por 13 hrs. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y la mezcla fue lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar metil 2-[5-ciano-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato.

^{1}H-RMN ($CDCl_3$) δ:1,03 (6H; d; J = 6,8 Hz); 2,26-2,37 (1H; m); 2,44 (3H; s); 3,01 (2H; d; J = 7,4 Hz); 3,74 (3H; s); 7,08-7,14 (1H; m); 7,34 (2H; d; J = 7,9 Hz); 7,42 (1H; s); 7,48-7,61 (4H; m); 7,83-7,88 (1H; m).

4) El metil 2-[5-(aminometil)-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato fue obtenido como un

producto en bruto de metil 2-[5-ciano-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato (1,80 g; 4,68 mmol) según un método similar al método del Ejemplo 1-4). El Metil 2-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato (1,70 g; rendimiento 74%) fue obtenido como un aceite incoloro del producto en bruto según un método similar al método del Ejemplo 2-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,43 (9H; s); 2,26-2,37 (1H; m); 2,41 (3H; s); 2,80 (2H; d; J = 7,4 Hz); 3,75 (3H; s); 4,32 (2H; d; J = 4,9 Hz); 4,42 (1H; brs); 7,21-7,27 (5H; m); 7,41-7,46 (1H; m); 7,52-7,58 (2H; m); 7,76 (1H; dd; J = 7,4; 1,1 Hz).

5) El dihidrocloruro de metil 2-[5-(aminometil)-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato (345 mg, rendimiento 95%) fue obtenido como polvo rosa pálido de metil 2-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato (383 mg; 0,786 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,18-2,32 (1H; m); 2,41 (3H; s); 2,89 (2H; d; J = 6,6 Hz); 3,69 (3H; s); 3,99-4,09 (2H; m); 7,36 (2H; d; J = 8,1 Hz); 7,43 (2H; d; J = 8,1 Hz); 7,49 (1H; s); 7,57-7,70 (2H; m); 7,76 (2H; d; J = 7,5 Hz); 8,51 (3H; brs).

Ejemplo 193

Dihidrocloruro de ácido 2-[5-(aminometil)-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoico

1) El ácido 2-[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoico (0,85 g; rendimiento 67%) fue obtenido como un aceite incoloro de metil 2-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoato (1,31 g; 2,69 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:1,02 (6H; d; J = 6,6 Hz); 1,42 (9H; s); 2,21-2,33 (1H; m); 2,44 (3H; s); 2,93 (2H; d; J = 7,4 Hz); 4,39 (2H; brs); 7,22 (2H; d; J = 8,1 Hz); 7,31 (2H; d; J = 7,9 Hz); 7,48 (1H; s); 7,54-7,66 (3H; m); 8,31 (1H; m).

2) El dihidrocloruro de ácido 2-[5-(Aminometil)-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoico (329 mg, rendimiento 81%) fue obtenido como polvo blanco de ácido 2-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoico (429 mg; 0,904 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,27-2,36 (1H; m); 2,41 (3H; s); 2,90 (2H; d; J = 6,6 Hz); 4,04 (2H; d; J = 5,1 Hz); 7,36 (2H; d; J = 8,3 Hz); 7,40-7,49 (3H; m); 7,54-7,70 (3H; m); 7,76-7,84 (1H; m); 8,44 (3H; brs).

Ejemplo 194

Dihidrocloruro de 2-[5-(aminometil)-6-isobutil-4-(4-

metilfenil)piridin-2-il]benzamida

1) Terc-butil {[6-[2-(aminocarbonil)fenil]-2-isobutil-4-(4-metilfenil)piridin-3-il]metil}carbamato (290 mg, rendimiento 69%) fue obtenido como un aceite incoloro de ácido 2-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-4-(4-metilfenil)piridin-2-il]benzoico (421 mg; 0,887 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,6 Hz); 1,43 (9H; s); 2,30-2,37 (1H; m); 2,41 (3H; s); 2,83 (2H; d; J = 7,4 Hz); 4,34 (2H; d; J = 4,7 Hz); 4,42 (1H; brs); 5,54 (1H; brs); 6,42 (1H; brs); 7,20 (2H; d; J = 8,3 Hz); 7,24-7,25 (3H; m); 7,42-7,53 (3H; m); 7,70-7,75 (1H; m).

2) El dihidrocloruro de 2-[5-(Aminometil)-6-isobutil-4-(4-metilfenil)piridin-2-il]benzamida (254 mg, rendimiento 93%) fue obtenido como polvo amarillo de terc-butil {[6-[2-(aminocarbonil)fenil]-2-isobutil-4-(4-metilfenil)piridin-3-il]metil}carbamato (290 mg; 0,612 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,01 (6H; d; J = 6,6 Hz); 2,27-2,37 (1H; m); 2,40 (3H; s); 2,90-2,99 (2H; m); 4,04 (2H; m); 7,36 (2H; d; J = 8,1 Hz); 7,41 (2H; d; J = 8,3 Hz); 7,50 (1H; s); 7,56-7,71 (4H; m); 7,92-8,01 (1H; m); 8,61 (3H; brs).

Ejemplo 195

Dihidrocloruro de 5-(aminometil)-N,N-diciclohexil-6-isobutil-

2-metil-4-(4-metilfenil)nicotinamida

1) El ácido 5-Ciano-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (2.16 g; rendimiento 85%) fue obtenido como polvo blanco de terc-butil 5-ciano-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (3,00 g; 8,23 mmol) según un método similar al método del Ejemplo 24-1).

^{1}H-RMN ($CDCl_3$) δ:1,00 (6H; d; J = 6,6 Hz); 2,17-2,32 (1H; m); 2,42 (3H; s); 2,67 (3H; s); 2,95 (2H; d; J = 7,4 Hz); 7,27-7,34 (4H; m).

2) A una solución de ácido 5-ciano-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (2,00 g; 6,49 mmol) en diclorometano fue agregado cloruro de oxalilo (0,68 mL; 7,78 mmol) y N,N-dimetilformamida (0,05 mL) y la mezcla fue agitada a la temperatura ambiente por 30 min. El solvente fue evaporado bajo presión reducida y el residuo fue disuelto en tetrahidrofurano. Subsiguientemente, trietilamina (1,8 mL; 13,0 mmol) y diciclohexilamina (1,55 mL; 7,78 mmol) fue agregado y la mezcla fue agitada a la temperatura ambiente por 30 min. La mezcla de reacción fue diluida con acetato de etilo (100 mL) y lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar 5-ciano-N,N-diciclohexil-6-isobutil-2-metil-4-(4-metilfenil)nicotinamida (0,35 g; rendimiento 11%)

como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,79-0,96 (4H; m); 1,01 (6H; dd; J = 11,1; 6,6 Hz); 1,07-1,34 (4H; m); 1,40-1,53 (5H; m); 1,58-1,68 (4H; m); 1,72-1,84 (3H; m); 2,22-2,31 (1H; m); 2,40 (3H; s); 2,59 (3H; s); 2,69-2,79 (2H; m); 2,87-3,04 (2H; m); 7,25 (2H; d; J = 8,5 Hz); 7,46 (2H; d; J = 8,1 Hz).

3) El dihidrocloruro de 5-(Aminometil)-N,N-diciclohexil-6-isobutil-2-metil-4-(4-metilfenil)nicotinamida (0,20 g; rendimiento 49%) fue obtenido como polvo amarillo de 5-ciano-N,N-diciclohexil-6-isobutil-2-metil-4-(4-metilfenil)nicotinamida (0,35 g; 0,742 mmol) según un método similar al método del Ejemplo 108-3).

^{1}H-RMN (DMSO-d_6) δ:0,73-0,88 (2H; m); 0,90-1,15 (12H; m); 1,24-1,75 (10H; m); 2,13-2,27 (3H; m); 2,36 (3H; s); 2,78-2,86 (2H; m); 2,88-2,95 (2H; m); 3,68-3,81 (1H; m); 3,96-4,09 (1H; m); 7,26-7,37 (4H; m).

Ejemplo 196

Dihidrocloruro de metil 1-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}piperidin-4-carboxilato

1) El metil 1-{[5-ciano-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}piperidin-4-carboxilato (3,20 g; rendimiento 91%) fue obtenido como un aceite incoloro de ácido 5-ciano-6-isobutil-2-metil-4-(4-

metilfenil)nicotínico (2,50 g; 8,1 mmol) e isonipecotato de metilo (1,3 mL; 9,73 mmol) según un método similar al método del Ejemplo 195-2).

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; dd; J = 12,1; 6,6 Hz); 1,42-1,85 (4H; m); 2,19-2,37 (3H; m); 2,40 (3H; s); 2,55-2,60 (3H; m); 2,61-3,20 (5H; m); 3,63-3,66 (3H; m); 4,23-4,45 (1H; m); 7,25-7,42 (4H; m).

2) El dihidrocloruro de metil 1-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}piperidin-4-carboxilato (3,27 g; rendimiento 87%) fue obtenido como polvo blanco de metil 1-{[5-ciano-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}piperidin-4-carboxilato (3,20 g; 7,38 mmol) según un método similar al método del Ejemplo 108-3).

^{1}H-RMN (DMSO-d_6) δ:0,67-0,90 (1H; m); 0,98 (6H; t; J = 5,9 Hz); 1,25-1,76 (3H; m); 2,16-2,28 (1H; m); 2,36-2,37 (3H; m); 2,63-2,76 (1H; m); 2,90-3,03 (2H; m); 3,17-3,34 (1H; m); 3,57 (3H; s); 3,58-3,60 (2H; m); 3,68-3,97 (2H; m); 4,05-4,10 (1H; m); 7,11-7,36 (4H; m); 8,34 (3H; brs).

Ejemplo 197

Sal terc-butilamina de ácido 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico

El ácido 5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (0,10 g; 0,320 mmol) fue disuelto en

una mezcla de solvente de agua (1,5 mL)-acetonitrilo (1,5 mL) con calentamiento bajo reflujo por 10 min. La terc-butilamina (23,4 mg; 0,320 mmol) fue agregada a la solución obtenida y la mezcla fue agitada a la misma temperatura por 10 min. Fue agregado acetonitrilo (20 mL), y a la mezcla se le permitió enfriar a temperatura ambiente y fue agitada a 0°C por 30 min. El sólido precipitado fue recolectado por filtración y fue lavado con acetonitrilo (10 mL) para dar sal terc-butilamina de ácido 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (78,4 mg, rendimiento 63%) como un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ:0,91 (6H; d; J = 6,6 Hz); 1,12 (9H; s); 2,06-2,25 (1H; m); 2,31 (3H; s); 2,34 (3H; s); 2,66 (2H; d; J = 7,0 Hz); 3,31 (2H; brs); 3,37 (2H; s); 7,10 (2H; d; J = 8,1 Hz); 7,16 (2H; d; J = 8,1 Hz).

Ejemplo 198

Dihidrocloruro de ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(metiltio)metil]piridin-3-il}metil)amina

1) A una solución de metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilo (476 mg, 1 mmol) en tetrahidrofurano (5 mL) fue agregado 15% solución de metantiolato de sodio acuosa (3 mL) y la mezcla fue agitada a 50°C por 2 hrs. Fue agregada agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica

fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar terc-butil ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(metiltio)metil]piridin-3-il}metil)carbamato (312 mg, rendimiento 72%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 1,94 (3H; s); 2,12-2,23 (1H; m); 2,42 (3H; s); 2,67 (3H; s); 2,75 (2H; d; J = 6,9 Hz); 3,39 (2H; s); 4,02 (2H; d; J = 5,7 Hz); 4,19 (1H; brs); 7,04 (2H; d; J = 8,1 Hz); 7,24 (2H; d; J = 8,1 Hz).

2) El dihidrocloruro de ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(metiltio)metil]piridin-3-il}metil)amina (36 mg, rendimiento 96%) fue obtenido como polvo blanco del terc-butil ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(metiltio)metil]piridin-3-il}metil)carbamato según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 1,93 (3H; s); 2,12-2,19(1H; m); 2,42 (3H; s); 2,89 (3H; s); 3,08 (2H; brs); 3,48 (2H; s); 3,75 (2H; s); 7,28 (2H; d; J = 7,8 Hz); 7,39 (2H; d; J = 7,8 Hz); 8,36 (3H; brs).

Ejemplo 199

Dihidrocloruro de ({2-isobutil-6-metil-4-(4-metilfenil)-5-

[(metilsulfonil)metil]piridin-3-il}metil)amina

1) A una solución de terc-butil ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(metiltio)metil]piridin-3-il}metil)carbamato (200 mg; 0,46 mmol) en metanol-agua (10:1, 5 mL) fue agregado "Oxone" (marca de fábrica, 310 mg) y luego fue agregado ácido sulfúrico (50 ml). La mezcla fue agitada a la temperatura ambiente por 6 hrs. El carbonato hidrógeno de sodio saturado acuoso fue agregado a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar terc-butil ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(metilsulfonil)metil]piridin-3-il}metil)carbamato (128 mg, rendimiento 60%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,19-2,28 (1H; m); 2,41 (3H; s); 2,61 (3H; s); 2,74 (3H; s); 2,75 (2H; d; J = 7,2 Hz); 4,25 (2H; d; J = 5,1 Hz); 4,24 (1H; brs); 4,26 (2H; s); 7,71 (2H; d; J =7,8 Hz); 7,26 (2H; d; J = 8,1 Hz).

2) El dihidrocloruro de ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(metilsulfonil)metil]piridin-3-il}metil)amina (36 mg, rendimiento 96%) fue obtenido como polvo blanco del terc-butil ({2-isobutil-6-metil-4-(4-metilfenil)-5-

[(metilsulfonil)metil]piridin-3-il}metil)carbamato según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,17-2,24 (1H; m); 2,40 (3H; s); 2,81 (3H; s); 2,87 (3H; s); 2,89 (2H; brs); 3,68 (2H; brs); 4,40 (2H; s); 7,24 (2H; d; J = 8,1 Hz); 7,35 (2H; d; J = 7,8 Hz); 8,20 (3H; brs).

Ejemplo 200

Dihidrocloruro de ácido ({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)acético

1) A una solución de metansulfonato de [5-({[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilo (952 mg, 2 mmol) en N,N-dimetilformamida (5 mL) fue agregado carbonato de potasio (415 mg, 3 mmol) y entonces fue agregado mercaptoacetato de etilo (240 µL; 2,2 mmol). La mezcla fue agitada a 50°C por 1 hr. Fue agregado el agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue disuelto en etanol (5 mL). Fue agregada solución 1N de hidróxido de sodio acuosa (5 mL) y la mezcla fue agitada a la temperatura ambiente por 2 hrs. Fue agregado 1N de ácido clorhídrico (5 mL) a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La

capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar ácido ({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)acético (265 mg, rendimiento 27%) como un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ:0,91 (6H; d; J = 6,6 Hz); 1,34 (9H; s); 2,13-2,27 (1H; m); 2,37 (3H; s); 2,55 (2H; d; J = 6,0 Hz); 2,58 (3H; s); 3,09 (2H; s); 3,50 (2H; s); 3,74 (2H; d; J = 4,2 Hz); 6,81 (1H; brs); 7,18 (2H; d; J = 8,1 Hz); 7,24 (2H; d; J = 8,1 Hz); 12,49 (1H; brs).

2) Dihidrocloruro de ácido ({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)acético (106 mg, rendimiento 96%) fue obtenido como polvo blanco de ácido ({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)acético según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,14-2,25 (1H; m); 2,42 (3H; s); 2,85 (3H; brs); 3,01 (2H; s); 3,20 (2H; s); 3,59 (2H; s); 3,70 (2H; s); 7,26 (2H; d; J = 8,1 Hz); 7,37 (2H; d; J = 8,1 Hz); 8,23 (3H; brs).

Ejemplo 201

Dihidrocloruro de ácido ({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}sulfonil)acético

1) A una solución de ácido ({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)acético (260 mg, 0.55 mmol) en metanol-agua (10:1, 5 mL) fue agregado "Oxone" (marca de fábrica, (508 mg) y entonces fue agregado ácido sulfúrico (50 ml). La mezcla fue agitada a la temperatura ambiente por 6 hrs. Fue agregado carbonato de hidrógeno de sodio saturado acuoso a la mezcla de reacción y la mezcla se extrajo coh acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar un aceite. El dihidrocloruro de ácido ({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}sulfonil)acético (104 mg, rendimiento 68%) fue obtenido como polvo blanco del aceite obtenido según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,95 (6H; d; J = 6,6 Hz); 2,21-2,28 (1H; m); 2,39 (3H; s); 2,65 (3H; s); 2,74 (2H; s); 3,61(2H; s); 4,13 (2H; s); 4,55 (2H; s); 7,18 (2H; d; J = 8,1 Hz); 7,29 (2H; d; J = 7,8 Hz); 8,01 (3H; brs).

Ejemplo 202

dihidrocloruro de {[2-isobutil-6-metil-4-(4-metilfenil)-5-

(1H-tetrazol-5-ilmetil)piridin-3-il]metil}amina

1) A una solución de terc-butil {[5-(cianometil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (300 mg; 0,74 mmol) en tolueno (5 mL) fue agregado óxido de dibutilestaño (37 mg; 0,15 mmol) y trimetilsilil azida (292 mL; 2,2 mmol) y la mezcla fue agitada a 80°C durante 3 días. Fue agregada agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar terc-butil {[2-isobutil-6-metil-4-(4-metilfenil)-5-(1H-tetrazol-5-ilmetil)piridin-3-il]metil}carbamato (229 mg, rendimiento 69%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,90 (6H; d; J = 6,6 Hz); 1,36 (9H; s); 2,08-2,11 (1H; m); 2,35 (3H; s); 2,42 (3H; s); 2,83 (2H; s); 4,03(2H; s); 4,09 (2H; brs); 4,79 (1H; brs); 7,01 (2H; d; J = 8,1 Hz); 7,18 (2H; d; J = 7,8 Hz).

2) Dihidrocloruro de {[2-isobutil-6-metil-4-(4-metilfenil)-5-(1H-tetrazol-5-ilmetil)piridin-3-il]metil}amina (181 mg, rendimiento 87%) fue obtenido como polvo blanco del terc-butil {[2-isobutil-6-metil-4-(4-metilfenil)-5-(1H-tetrazol-5-ilmetil)piridin-3-il]metil}carbamato según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,15-2,23 (1H; m); 2,36 (3H; s); 2,74 (3H; s); 3,14 (2H; s); 3,78 (2H; s); 4,04 (2H; s); 7,06 (2H; d; J = 8,1 Hz); 7,28 (2H; d; J = 8,1 Hz); 8,35 (3H; brs).

Ejemplo 203

Dihidrocloruro de 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}-1,2,4-oxadiazol-5(4H)-ona

1) A una solución de terc-butil {[5-(cianometil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (400 mg; 1;0 mmol) en etanol (5 mL) fue agregado carbonato de sodio (420 mg; 4,0 mmol) y cloruro de hidroxiamonio (210 mg; 3,0 mmol) y la mezcla fue agitada a 80°C durante 3 días. Fue agregada agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue disuelto en tetrahidrofurano (5 mL). Fue agregado N,N'-carbonildiimidazol (350 mg; 2,5 mmol) y la mezcla fue agitada a 80°C por 4 hrs. La mezcla de reacción fue concentrada y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar terc-butil ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-il)metil]piridin-3-il}metil)carbamato (120 mg, rendimiento 26%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,95 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,06-2,22 (1H; m); 2,40 (3H; s); 2,51 (3H; s); 2,73 (2H; d; J = 7,2 Hz); 3,62(2H; s); 4,02 (2H; d; J = 4,5 Hz); 4,45 (1H; brs); 7,02 (2H; d; J = 8,1 Hz); 7,26 (2H; d; J = 7,8 Hz).

2) Un dihidrocloruro de (181 mg, rendimiento 87%) fue obtenido como polvo blanco de terc-butil ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-il)metil]piridin-3-il}metil)carbamato según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,13-2,21 (1H; m); 2,39 (3H; s); 2,75 (3H; s); 3,05 (2H; brs); 3,66 (2H; s); 3,76 (2H; brs); 7,16 (2H; d; J = 7,8 Hz); 7,36 (2H; d; J = 7,8 Hz); 8,26 (3H; brs).

Ejemplo 204

Dihidrocloruro de dietil {[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}fosfonato

1) El fosfito de trietilo (772 mL; 4,5 mmol) fue agregado a metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilo (692 mg; 1,45 mmol) y la mezcla fue agitada a 150°C por 3 hrs. A la mezcla de reacción se le permitió enfriar a la temperatura ambiente y fue purificada por cromatografía en columna de gel de silice para dar dietil {[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-

metilfenil)piridin-3-il]metil}fosfonato (314 mg, rendimiento 42%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,95 (6H; d; J = 6,6 Hz); 1,17 (6H; t; J = 7,2 Hz); 1,38 (9H; s); 2,14-2,24 (1H; m); 2,40 (3H; s); 2,66 (3H; s); 2,73 (2H; d; J = 5,1 Hz); 2,96 (1H; s); 3,04 (1H; s); 3,86 (4H; q; J = 7,2 Hz); 4,00 (2H; d; J = 4,8 Hz); 4,17 (1H; brs); 7,07 (2H; d; J = 8,1 Hz); 7,24 (2H; d; J = 8,1 Hz).

2) El dihidrocloruro de dietil {[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}fosfonato (106 mg, rendimiento 96%) fue obtenido como polvo blanco del dietil {[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}fosfonato según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,3 Hz); 1,21 (6H; t; J = 7,2 Hz); 2,11-2,18 (1H; m); 2,42 (3H; s); 2,95 (3H; s); 3,09 (2H; s); 3,17 (2H; s); 3,78 (2H; s); 3,82 (4H; q; J = 7,2 Hz); 7,26 (2H; d; J = 7,8 Hz); 7,39 (2H; d; J = 7,8 Hz); 8,43 (3H, brs).

Ejemplo 205

Trihidrocloruro de piridin-2-ilmetil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) Piridin-2-ilmetil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,21 g;

rendimiento 99%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,00 g; 2,42 mmol), hidrobromuro de 2-(bromometil)piridina (0.92 g; 3.64 mmol) y carbonato de potasio (1,00 g; 7,27 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$)δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,14-2,25 (1H; m); 2,35 (3H; s); 2,56 (3H; s); 2,78 (2H; d; J = 7,2 Hz); 4,14 (2H; brs); 4,25 (1H; brs); 5,06 (2H; s); 6,89 (1H; d; J = 7,7 Hz); 7,06 (2H; d; J = 7,9 Hz); 7,13 (2H; d; J = 7,9 Hz); 7,17-7,22 (1H; m); 7,57 (1H; t; J = 7,7 Hz); 8,52 (1H; d; J = 4,7 Hz).

2) Trihidrocloruro de piridin-2-ilmetil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,23 g; rendimiento 99%) fue obtenido como un sólido blanco del piridin-2-ilmetil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,21 g; 2,40 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-MNR (DMSO-d_6) δ: 0,97 (6H; d; J = 6,4 Hz); 2,17-2,28 (1H; m); 2,34 (3H; s); 2,61 (3H; s); 2,94 (2H; d; J = 6,9 Hz); 3,81 (2H; d; J = 4,9 Hz); 5,20 (2H; s); 7,19 (4H; s); 7,23 (1H; brs); 7,62-7,66 (1H; m); 8,06 (1H; t; J = 7,9 Hz); 8,39 (3H; brs); 8,68 (1H; d; J = 4,9 Hz).

Ejemplo 206

Dihidrocloruro de bencil [5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato

1) El bencil [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (305 mg, rendimiento 84%) fue obtenido como polvo blanco de ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acético (300 mg; 0,703 mmol) y bromuro de bencilo (180 mg; 1,05 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,38 (9H; s); 2,12-2,28 (1H; m); 2,38 (3H; s); 2,49 (3H; s); 2,76 (2H; d; J = 6,6 Hz); 3,39 (2H; s); 4,03 (2H; d; J = 5,1 Hz); 4,20 (1H; brs); 5,05 (2H; s); 6,90 (2H; d; J = 7,9 Hz); 7,14 (2H; d; J = 7,9 Hz); 7,19-7,25 (2H; m); 7,31-7,40 (3H; m).

2) Dihidrocloruro de bencil [5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (214,5 mg; rendimiento 95%) fue obtenido como polvo blanco del bencilo [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (240 mg; 0,464 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,98 (6H; d; J = 6,6 Hz); 2,11-2,27 (1H; m); 2,38 (3H; s); 2,78 (3H; s); 3,15 (2H;s); 3,78 (2H; d; J = 5,1 Hz); 5,04 (2H; s); 7,10 (2H; d; J = 8,1 Hz); 7,20-7,45 (7H; m); 8,40 (3H; brs).

Ejemplo 207

dihidrocloruro de 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzamida

1) Terc-butil {[5-({[4-(aminocarbonil)fenil]tio}metil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (360 mg, rendimiento 72%) fue obtenido como un sólido blanco de ácido 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoico (0,50 g; 0,935 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,13-2,25 (1H; m); 2,38 (3H; s); 2,65 (3H; s); 2,76 (2H; d; J = 7,4 Hz); 3,85 (2H; s); 4,04 (2H; d; J = 5,1 Hz); 4,20 (1H; brs); 7,05 (2H; d; J = 7,4 Hz); 7,12 (2H; d; J = 8,5 Hz); 7,19 (2H; d; J = 7,9 Hz); 7,64 (2H; d; J = 8,5 Hz).

2) Dihidrocloruro de 4-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzamida (253 mg, rendimiento 74%) fue obtenido como un sólido blanco del terc-butil {[5-({[4-(aminocarbonil)fenil]tio}metil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (360 mg; 0,674 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,5 Hz); 2,13-2,22 (1H; m); 2,37 (3H; s); 2,86 (3H; brs); 3,14 (2H; brs); 3,78 (2H;

d; J = 4,7 Hz); 3,99 (2H; s); 7,22 (2H; d; J = 8,5 Hz); 7,26 (2H; d; J = 8,1 Hz); 7,33 (2H; d; J = 8,5 Hz); 7,37 (1H; brs) 7.98 (1H, brs), 8.39 (3H, brs).

Ejemplo 208

Dihidrocloruro de metil 2-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoato

1) El metil 2-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoato (1,19 g; rendimiento 86%) fue obtenido como un aceite incoloro del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,00 g; 2,51 mmol) y 2-mercaptobenzoato de metilo (422 mg, 2,51 mmol) según un método similar al método del Ejemplo 183-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,12-2,26 (1H; m); 2,35 (3H; s); 2,66 (3H; s); 2,75 (2H; d; J = 7,4 Hz); 3,77 (2H; s); 3,89 (3H; s); 4,03 (2H; d; J = 4,9 Hz); 4,19 (1H; brs); 7,05 (1H; d; J = 8,1 Hz); 7,09-7,13 (3H; m), 7,17 (2H; d; J = 8,1 Hz); 7,32-7,38 (1H; m); 7,93 (1H; dd; J = 7,7; 1,5 Hz).

2) Dihidrocloruro de metil 2-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoato (165 mg, rendimiento 91%) fue obtenido como un sólido blanco de metil 2-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoato (190

mg; 0,346 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,13-2,25 (1H; m); 2,34 (3H; s); 2,77 (3H; brs); 2,98 (2H; brs); 3,69-3,76 (2H; m); 3,80 (3H; s); 3,87 (2H; s); 7,22-7,27 (4H; m); 7,31 (2H; d; J = 8,5 Hz); 7,47-7,52 (1H; m); 7,87 (1H; dd; J = 7,7; 1,5 Hz); 8,18 (3H; brs).

Ejemplo 209

Ácido 2-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoico

1) El ácido 2-({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoico (0,86 g; rendimiento 88%) fue obtenido como un sólido blanco de metil 2-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoato (1,00 g; 1,82 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,13-2,24 (1H; m); 2,37 (3H; brs); 2,73 (3H; brs); 2,90 (2H; d; J = 7,0 Hz); 3,77 (2H; s); 4,05 (2H; d; J = 4,5 Hz); 4,32 (1H; brs); 7,01-7,10 (3H; m); 7,16-7,21 (3H; m); 7,30-7,36 (1H; m); 7,94-7,97 (1H; m).

2) El ácido 2-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoico (274 mg,

rendimiento 99%) fue obtenido como un sólido blanco de ácido 2-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoico (0,29 g; 0,542 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,4 Hz); 2,15-2,24 (1H; m); 2,34 (3H; s); 2,81 (3H; brs); 3,03 (2H; brs); 3,66-3,85 (4H; m); 7,19-7,35 (6H; m); 7,44-7,50 (1H; m); 7,88 (1H; d; J = 7,5 Hz); 8,23 (3H; brs).

Ejemplo 210

Dihidrocloruro de 2-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzamida

1) Terc-butil {[5-({[2-(aminocarbonil)fenil]tio}metil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,23 g; rendimiento 48%) fue obtenido como un sólido blanco de ácido 2-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoico (0,48 g; 0,898 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,14-2,26 (1H; m); 2,40 (3H; s); 2,64 (3H; s); 2,75 (2H; d; J = 7,4 Hz); 3,82 (2H; s); 4,00 (2H; d; J = 5,3 Hz); 4,27 (1H; brs); 5,39 (1H; brs); 6,68 (1H; brs); 6,99 (2H; d; J = 7,9 Hz); 7,19-7,34 (5H; m); 7,75-7,78 (1H; m).

2) Dihidrocloruro de 2-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzamide (218 mg, rendimiento 99%) fue obtenido como un sólido blanco de terc-butil {[5-({[2-(aminocarbonil)fenil]tio}metil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,23 g; 0,431 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,10-2,24 (1H; m); 2,38 (3H; s); 2,83 (3H; s); 3,18 (2H; brs); 3,79 (2H; d; J = 5,1 Hz); 3,86 (2H; s); 7,16 (2H; d; J = 7,7 Hz); 7,23-7,36 (6H; m); 7,42 (1H; brs); 7,48 (1H; dd; J = 7,4; 1,4 Hz), 7,84 (1H; brs); 8,41 (3H; brs).

Ejemplo 211

Dihidrocloruro de metil 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoato

1) El metil 3-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoato (1,35 g; rendimiento 82%) fue obtenido como un sólido castaño de terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,20 g; 3,01 mmol) y 3-mercaptobenzoato de metilo (507 mg, 3,01 mmol) según un método similar al método del Ejemplo 183-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,15-

2,24 (1H; m); 2,38 (3H; s); 2,64 (3H; s); 2,75 (2H; d; J = 7,4 Hz); 3,83 (2H; s); 3,90 (3H; s); 4,02 (2H; d; J = 5,1 Hz); 4,22 (1H; brs); 7,00 (2H; d; J = 8,1 Hz); 7,18 (2H; d; J = 7,7 Hz); 7,28-7,30 (1H; m); 7,76-7,79 (1H; m); 7,80-7,84 (1H; m).

2) El dihidrocloruro de metil 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoato (268 mg, rendimiento 87%) fue obtenido como un sólido blanco de metil 3-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoato (324 mg; 0,590 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,11-2,23 (1H; m); 2,36 (3H; s); 2,75 (3H; s); 2,97 (2H; brs); 3,74 (2H; d; J = 4,5 Hz); 3,85 (3H; s); 3,96 (2H; s); 7,19 (2H; d; J = 7,4 Hz); 7,29 (2H; d; J = 7,9 Hz); 7,43 (2H; d; J = 5,1 Hz); 7,65 (1H; s); 7,79-7,83 (1H; m); 8,18 (3H; brs).

Ejemplo 212

Dihidrocloruro de ácido 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoico

1) El ácido 3-({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoico (0,73 g; rendimiento 73%) fue obtenido como un sólido blanco de metil 3-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-

metilfenil)piridin-3-il]metil}tio)benzoato (0,90 g; 1,64 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,13-2,26 (1H; m); 2,38 (3H; s); 2,68 (3H; s); 2,79 (2H; d; J = 7,0 Hz); 3,85 (2H; s); 4,04 (2H; d; J = 4,9 Hz); 4,24 (1H; brs); 7,00 (2H; d; J = 7,2 Hz); 7,19 (2H; d; J = 7,9 Hz); 7,30-7,35 (2H; m); 7,84 (1H; brs), 7,89 (1H; brs).

2) El dihidrocloruro de ácido 3-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoico (167 mg, rendimiento 80%) fue obtenido como un sólido blanco de ácido 3-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoico (0,22 g; 0,441 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,11-2,22 (1H; m); 2,37 (3H; s); 2,84 (3H; brs); 3,10 (2H; brs); 3,76 (2H; d; J = 5,1 Hz); 3,97 (2H; s); 7,21 (2H; d; J = 7,9 Hz); 7,30 (2H; d; J = 7,9 Hz); 7,41-7,42 (2H; m); 7,65 (1H; s); 8,38 (3H, brs).

Ejemplo 213

Dihidrocloruro de 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzamida

1) Terc-butil {[5-({[3-(aminocarbonil)fenil]tio}metil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato

(460 mg, rendimiento 92%) fue obtenido como un sólido blanco de ácido 3-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzoico (0,50 g; 0,935 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,16-2,27 (1H; m); 2,38 (3H; s); 2,65 (3H; s); 2,75 (2H; d; J = 7,2 Hz); 3,84 (2H; s); 4,02 (2H; d; J = 5,1 Hz); 4,24 (1H; brs); 6,99 (2H; d; J = 7,9 Hz); 7,19 (2H; d; J = 7,7 Hz); 7,25-7,31 (2H; m); 7,49-7,53 (1H; m); 7,56-7,59 (1H; m).

2) El dihidrocloruro de 3-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)benzamida (439 mg; cuantitativo) fue obtenido como un sólido blanco del terc-butil {[5-({[3-(aminocarbonil)fenil]tio}metil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (460 mg; 0,862 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,13-2,22 (1H; m); 2,38 (3H; s); 2,86 (3H; s); 3,19 (2H; d; J = 6,6 Hz); 3,78 (2H; d; J = 4,9 Hz); 3,98 (2H; s); 7,23 (2H; d; J = 8,1 Hz); 7,31-7,39 (4H; m); 7,45 (1H; brs); 7,70 (1H; brs); 7,75 (1H; d; J = 7,4 Hz); 8,04 (1H; brs); 8,46 (3H; brs).

Ejemplo 214

Dihidrocloruro de ácido 4-{[5-(aminometil)-6-isobutil-2-

metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoico

1) A una solución de terc-butilo {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,50 g; 1,05 mmol), 4-hidroxibenzoato de metilo (0,16 g; 1,05 mmol) y trifenilfosfina (0,36 g; 1,37 mmol) en tetrahidrofurano (10 mL) fue agregado solución 40% (0,60 mL; 1,37 mmol) de azodicarboxilato de dietilo en tolueno y la mezcla fue agitada a la temperatura ambiente por 30 min. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar metil 4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoato (380 mg, rendimiento 68%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,16-2,27 (1H; m); 2,34 (3H; s); 2,62 (3H; s); 2,80 (2H; d; J = 7,4 Hz); 3,87 (3H; s); 4,08-4,13 (2H; m); 4,30 (1H; brs); 4,68 (2H; s); 6,80 (2H; d; J = 8,9 Hz); 7,04 (2H; d; J = 7,9 Hz); 7,16 (2H; d; J = 7,7 Hz); 7,93 (2H; d; J = 8,9 Hz).

2) El ácido 4-{[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoico (300 mg, rendimiento 81%) fue obtenido como un sólido blanco de metil 4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoato (380 mg; 0,713 mmol) según un método similar al método del

Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:1,00 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,17-2,29 (1H; m); 2,35 (3H; s); 2,66 (3H; brs); 2,84 (2H; brs); 4,08-4,14 (2H; m); 4,22-4,25 (1H; m); 4,70 (2H; s); 6,82 (2H; d; J = 8,9 Hz); 7,04 (2H; d; J = 7,9 Hz); 7,17 (2H; d; J = 7,9 Hz); 7,99 (2H; d; J = 8,9 Hz).

3) El dihidrocloruro de ácido 4-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoico (267 mg, rendimiento 94%) fue obtenido como un sólido blanco de ácido 4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoico (0,30 g; 0,578 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN ($CDCl_3$) δ:1,00 (6H; d; J = 6,6 Hz); 2,17-2,26 (1H; m); 2,34 (3H; s); 2,82 (3H; brs); 3,11 (2H; brs); 3,83 (2H; d; J = 5,3 Hz); 4,79 (2H; s); 6,93 (2H; d; J = 8,9 Hz); 7,26 (2H; d; J = 8,1 Hz); 7,31 (2H; d; J = 8,1 Hz); 7,85 (2H; d; J = 8,9 Hz); 8,35 (3H; brs).

Ejemplo 215

Dihidrocloruro de metil 4-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoato

Dihidrocloruro de metil 4-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoato (281 mg, rendimiento 99%) fue obtenido como un sólido blanco de metil

4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoato (0,30 mg; 0,563 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,18-2,27 (1H; m); 2,33 (3H; s); 2,82 (3H; brs); 3,11 (2H; brs); 3,81-3,83 (5H; m); 4,80 (2H; s); 6,96 (2H; d; J = 8,9 Hz); 7,26 (2H; d; J = 7,9 Hz); 7,30 (2H; d; J = 8,1 Hz); 7,87 (2H; d; J = 8,9 Hz); 8,38 (3H; brs).

Ejemplo 216

Dihidrocloruro de {[2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}amina

1) A una solución de p-tolualdehído (8,5 g; 78,3 mmol) y acetona (10 mL) en agua (200 mL) fue agregado hidróxido de sodio (3,13 g; 78,3 mmol) y la mezcla fue agitada a la temperatura ambiente durante 3 días. La mezcla de reacción fue diluída con acetato de etilo, lavada consecutivamente con agua y solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida para dar 4-(4-metilfenil)but-3-en-2-ona (9,2 g; rendimiento 80%) como un aceite. El aceite obtenido (1,0 g; 6,24 mmol) fue disuelto en etanol (20 mL) y 3-amino-5-metilhex-2-ennitrilo (0,93 g; 7,49 mmol) y fue agregado hidróxido de sodio (0,3 g; 7,49 mmol). La mezcla fue calentada bajo reflujo por 2 hrs. La mezcla de reacción fue diluída con acetato de etilo, lavada consecutivamente con

solución de cloruro de amonio acuosa saturada y solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida para dar un residuo. El 2-isobutil-6-metil-4-(4-metilfenil)nicotinonitrilo (0,45 g; rendimiento 27%) fue obtenido como un aceite amarillo del residuo obtenido según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,6 Hz); 2,20-2,33 (1H; m); 2,43 (3H; s); 2,63 (3H; s); 2,96 (2H; d; J = 7,4 Hz); 7,11 (1H; s); 7,31 (2H; d; J = 7,9 Hz); 7,47 (2H; d; J = 8,3 Hz).

2) El dihidrocloruro de {[2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}amina (456 mg, rendimiento 78%) fue obtenido como un sólido blanco de 2-isobutil-6-metil-4-(4-metilfenil)nicotinonitrilo (0,45 g; 1,70 mmol) según un método similar al método del Ejemplo 108-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,4 Hz); 2,13-2,22 (1H; m); 2,41 (3H; s); 2,72-2,82 (3H; m); 3,05-3,18 (2H; m); 4,02-4,11 (2H; m); 7,41 (4H; s); 7,67 (1H; brs); 8,47-8,58 (3H; m).

Ejemplo 217

4-metilbencensulfonato de ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]piridin-3-il}metil)amina

1) A una solución de 4-metilbencensulfinato de sodio (9,00

g; 50,5 mmol) en etanol (50 mL) fue agregado bromoacetona (6,9 g; 50 mmol) y la mezcla fue calentada bajo reflujo por 30 min. La mezcla de reacción fue dividida entre acetato de etilo y agua. La capa orgánica fue lavada con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de silice para dar 1-[(4-metilfenil)sulfonil]acetona (8,0 g; rendimiento 75%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$)δ: 2,41 (3H; s); 2,46 (3H; s); 4,14 (2H; s); 7,37 (2H; d; J = 8,2 Hz); 7,77 (2H; d; J = 8,2 Hz).

2) Una mezcla de 1-[(4-metilfenil)sulfonil]acetona (2,0 g; 9,4 mmol); p-tolualdehído (1,1 g; 9,4 mmol); piperidina (0,093 mL; 0,94 mmol), ácido acético (0,11 mL; 1,9 mmol) y tolueno (100 mL) fue calentada bajo reflujo usando una trampa Dean-Stark por 3 hrs. A la mezcla de reacción se le permitió enfriar a la temperatura ambiente, fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida para dar 4-(4-metilfenil)-3-[(4-metilfenil)sulfonil]but-3-en-2-ona como un producto en bruto (3,5 g). Una mezcla del producto en bruto (1,73 g), 3-amino-5-metilhex-2-ennitrilo (0,65 g; 5,23 mmol) y etanol (50 mL) fue calentada bajo reflujo por 12 hrs. A la mezcla de reacción se le permitió enfriar a la temperatura ambiente, y el solvente fue

evaporado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice y el sólido obtenido fue recristalizado del diisopropil éter-acetato de etilo de para dar 2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]-1,4-dihidropiridin-3-carbonitrilo (1,3 g; rendimiento 64%) como un polvo blanco.

Punto de fusión: 135-137°C

3) 2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]nicotinonitrilo (0,77 g; rendimiento 68%) fue obtenido como polvo blanco de 2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]-1,4-dihidropiridin-3-carbonitrilo (1,1 g; 2,7 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$)δ: 0,99 (6H; d; J = 6,6 Hz); 2,20-2,35 (1H; m); 2,38 (3H; s); 2,39 (3H; s); 2,91 (2H; d; J = 7,2 Hz); 3,07 (3H; s); 6,86 (2H; d; J = 8,1 Hz); 7,08 (4H; d; J = 8,1 Hz); 7,23 (2H; d; J = 8,1 Hz).

4) ((2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]piridin-3-il)metil)amina (0,64 g; rendimiento 93%) fue obtenido como un aceite incoloro de 2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]nicotinonitrilo (0,69 g; 1,6 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$)δ: 0,96 (6H; d; J = 6,6 Hz); 1,41 (2H; brs);

2,20-2,35 (1H; m); 2,38 (6H; s); 2,79 (2H; d; J = 7,2 Hz); 2,96 (3H; s); 3,40 (2H; s); 6,76 (2H; d; J = 8,1 Hz); 7,03 (2H; d; J = 8,3 Hz); 7,09 (2H; d; J = 8,1 Hz); 7,27 (2H; d; J = 8,3 Hz).

5) ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]piridin-3-il}metil)amina (0,64 g; 1,5 mmol) fue disuelto en etanol (5 mL) y una solución hidrato del ácido p-toluensulfónico (0,29 g; 1,5 mmol) en etanol (5 mL) fue agregado por gotas con agitación a la temperatura ambiente. La mezcla fue agitada a la temperatura ambiente por 10 min. El precipitado fue recolectado por filtración, fue lavado con etanol enfriado y secado para dar ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-metilfenil)sulfonil]piridin-3-il}metil)amina 4-metilbencensulfonato (0,57 g; rendimiento 63%) como un polvo blanco.

^{1}H-RMN (DMSO-d_6)δ: 0,94 (6H; d; J = 6,6 Hz); 2,15-2,30 (1H; m); 2,29 (3H; s); 2,37 (6H; s); 2,78 (2H; d; J = 7,0 Hz); 2,84 (3H; s); 3,57 (2H; s); 6,87 (2H; d; J = 7,9 Hz); 7,11 (4H; d; J = 8,5 Hz); 7,25-7,30 (4H; m); 7,47 (2H; d; J = 7,9 Hz); 7,76 (3H, brs).

Ejemplo 218

{[2-isobutil-6-metil-4-(4-metilfenil)-5-(metilsulfonil)piridin-3-il]metil}amina

1) A una mezcla de 1-(metilsulfonil)acetona (3,68 g; 27

mmol), p-tolualdehido (3,24 g; 27 mmol), piperidina (0,26 mL; 2,7 mmol), ácido acético (0,31 mL; 5,4 mmol) y tolueno (200 mL) fue calentada bajo reflujo usando una trampa Dean-Stark por 12 hrs. A la mezcla de reacción se le permitió enfriar a la temperatura ambiente, fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue disuelto en metanol (20 mL). Fue agregado 3-amino-5-metilhex-2-ennitrilo (4,3 g; 35 mmol) y la mezcla fue calentada bajo reflujo por 6 hrs. La mezcla de reacción fue concentrada bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar 2-isobutil-6-metil-4-(4-metilfenil)-5-(metilsulfonil)-1,4-dihidropiridin-3-carbonitrilo (6.38 g; rendimiento 68%) como un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ:0,95 (3H; d; J = 6,6 Hz); 1,01 (3H; d; J = 6,6 Hz); 2,18-2,25 (1H; m); 2,32 (3H; s); 2,35 (3H; s); 2,40 (3H; s); 2,44 (1H; s); 3,04 (1H; s); 4,69 (1H; s); 5,80 (1H; s); 7,14 (2H; d; J = 8,1 Hz); 7,21 (2H; d; J = 8,3 Hz).

2) 2-isobutil-6-metil-4-(4-metilfenil)-5-(metilsulfonil)nicotinonitrilo (4,14 g; rendimiento 65%) fue obtenido como un sólido blanco de 2-isobutil-6-metil-4-(4-metilfenil)-5-(metilsulfonil)-1,4-dihidropiridin-3-carbonitrilo (6,38 g; 18,6 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$) δ:1,02 (6H; d; J = 6,8 Hz); 2,23-2,37 (1H; m); 2,44 (3H; s); 2,95 (2H; d; J = 7,2 Hz); 3,05 (3H; s); 7,24 (2H; d; J = 8,1 Hz); 7,33 (2H; d; J = 7,9 Hz).

3) {[2-isobutil-6-metil-4-(4-metilfenil)-5-(metilsulfonil)piridin-3-il]metil}amina (0,81 g; rendimiento 75%) fue obtenido como un sólido blanco de 2-isobutil-6-metil-4-(4-metilfenil)-5-(metilsulfonil)nicotinonitrilo (1,06 g; 3,09 mmol) de acuerdo a un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,8 Hz); 2,22-2,36 (1H; m); 2,43 (3H; s); 2,80 (3H; s); 2,82 (2H; d; J = 7,4 Hz); 2,96 (3H; s); 3,50 (2H; s); 7,12 (2H; d; J = 7,9 Hz); 7,26 (2H; d; J = 7,7 Hz).

Ejemplo 219

Dihidrocloruro de metil 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoato

1) Metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoato (730 mg, rendimiento 72%) fue obtenido como un aceite incoloro del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,75 g; 1,89 mmol) y 3-hidroxibenzoato de metilo (0,29 g; 1,90 mmol) según un método similar al método del Ejemplo 214-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,19-

2,28 (1H; m); 2,35 (3H; s); 2,62 (3H; s); 2,79 (2H; d; J = 7,2 Hz); 3,89 (3H; s); 4,07-4,11 (2H; m); 4,67 (2H; s); 6,98-7,02 (1H; m); 7,05 (2H; d; J = 7,9 Hz); 7,16 (2H; d; J = 7,7 Hz); 7,29-7,32 (1H; m); 7,42-7,43 (1H; m); 7,60-7,63 (1H; m).

2) Dihidrocloruro de metil 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoato (116 mg, rendimiento 85%) fue obtenido como un sólido blanco de metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoato (144 mg; 0,270 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,17-2,26 (1H; m); 2,34 (3H; s); 2,83 (3H; brs); 3,11 (2H; brs); 3,83 (5H; s); 4,79 (2H; s); 7,15 (1H; dd; J = 7,8; 2,2 Hz); 7,27 (2H; d; J = 8,3 Hz); 7,29-7,35 (3H; m); 7,42 (2H; t; J = 7,9 Hz); 7.56 (1H, d, J = 7.7 Hz), 8.38 (3H, brs).

Ejemplo 220

Dihidrocloruro de ácido 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoico

1) El ácido 3-{[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoico (460 mg, rendimiento 80%) fue obtenido como un aceite incoloro de metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoato (0,58 g; 1,10 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,17-2,28 (1H; m); 2,34 (3H; s); 2,65 (3H; s); 2,82 (2H; d; J = 7,2 Hz); 4,11 (2H; brs); 4,28 (1H; brs); 4,68 (2H; s); 7,03-7,07 (3H; m); 7,16 (2H; d; J = 7,9 Hz); 7,33 (1H; t; J = 8,0 Hz); 7,47 (1H; brs); 7,64-7,70 (1H; m).

2) El dihidrocloruro de ácido 3-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoico (128 mg, rendimiento 99%) fue obtenido como un sólido blanco de ácido 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoico (136 mg, 0,262 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,2 Hz); 2,18-2,27 (1H; m); 2,34 (3H; s); 2,73-2,79 (3H; m); 3,04 (2H; brs); 3,81 (2H; brs); 4,76 (2H; s); 7,11 (2H; d; J = 8,1 Hz); 7,21-7,31 (5H; m); 7,38 (1H; t; J = 7,7 Hz); 7,54 (1H; d; J = 7,5 Hz); 8.27 (3H, brs).

Ejemplo 221

Dihidrocloruro de metil 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoato

1) El metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoato (700 mg, rendimiento 70%) fue obtenido como un sólido blanco del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-

metilfenil)piridin-3-il]metil}carbamato (0,75 g; 1,89 mmol) y 2-hidroxibenzoato de metilo (0,29 g; 1,90 mmol) según un método similar al método del Ejemplo 214-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,19-2,28 (1H; m); 2,36 (3H; s); 2,67 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 3,81 (3H; s); 4,09 (2H; d; J = 4,0 Hz); 4,23 (1H; brs); 4,71 (2H; s); 6,66 (1H; d; J = 8,3 Hz); 6,93-6,98 (1H; m); 7,04 (2H; d; J = 8,1 Hz); 7,16 (2H; d; J = 7,7 Hz); 7,29-7,35 (1H; m); 7,72 (1H; dd; J = 7,6; 1,8 Hz).

2) Dihidrocloruro de metil 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoato (42.3 mg, rendimiento 56%) fue obtenido como un sólido blanco de metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoato (78,8 mg; 0,148 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,18-2,29 (1H; m); 2,36 (3H; s); 2,83 (3H; brs); 3,07 (2H; brs); 3,74 (3H; s); 3,83 (2H; d; J = 4,7 Hz); 4,78 (2H; s); 6,91 (1H; d; J = 8,5 Hz); 7,03 (2H; t; J = 7,4 Hz); 7,25 (2H; d; J = 7,9 Hz); 7,30 (2H; d; J = 8,1 Hz); 7,42-7,48 (1H; m); 7,64 (1H; dd; J = 7,6; 1,6 Hz); 8,30 (3H; brs).

Ejemplo 222

Dihidrocloruro de ácido 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoico

1) El ácido 2-{[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoico (140 mg, rendimiento 23%) fue obtenido como un sólido blanco de metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoato (0,62 g; 1,17 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,21-2,30 (1H; m); 2,34 (3H; s); 2,65 (3H; s); 2,81 (2H; d; J = 7,4 Hz); 4,10 (2H; d; J = 5,3 Hz); 4,92 (2H; s); 6,83 (1H; d; J = 8,3 Hz); 7,01 (2H; d; J = 8,1 Hz); 7,10-7,15 (1H; m); 7,17 (2H; d; J = 7,7 Hz); 7,44-7,50 (1H; m); 8,17 (1H; dd; J = 7,8; 1,8 Hz).

2) El dihidrocloruro de ácido 2-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoico (103 mg, rendimiento 77%) fue obtenido como un sólido blanco de ácido 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoico (0,14 g; 0,270 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,18-2,27 (1H; m); 2,37 (3H; s); 2,89 (3H; brs); 3,13 (2H; brs); 3,84 (2H; d; J = 4,7 Hz); 4,78 (2H; s); 6,86 (1H; d; J = 8,5 Hz); 7,02 (1H; t; J = 7,4 Hz); 7,27 (2H; d; J = 7,9 Hz); 7,32 (2H; d; J

= 8,1 Hz); 7,38-7,44 (1H; m); 7,61 (1H; dd; J = 7,5; 1,7 Hz); 8,39 (3H; brs).

Ejemplo 223

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]benzamida

A una solución de terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) en tetrahidrofurano (3 mL) fue agregado el cloruro de benzoilo (88 mL; 0,75 mmol) y fue agregada trietilamina (140 mL; 1,0 mmol). La mezcla fue agitada por 30 min. La solución de hidróxido de sodio acuosa saturada (5 mL) fue agregada a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar un aceite. A una solución del aceite obtenido en el acetato de etilo (1 mL) fue agregada una solución 4N ácido clorhídrico acetato de etilo (1 mL) y la mezcla fue agitada a la temperatura ambiente por 1 hr. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue cristalizado del hexano para dar dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]benzamida (203 mg, rendimiento 96%) como un polvo blanco.

^{1}H-RMN (DOSO-d_6)δ:1,00 (6H; d; J = 6,6 Hz); 2,20-2,32 (1H; m); 2,31 (3H; s); 2,64 (3H; s); 3,11 (2H; s); 3,87 (2H; s); 7,17-7,66 (9H; m); 8,49 (3H; brs); 10,13 (1H; brs).

Ejemplo 224

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2-fenilacetamida

Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2-fenilacetamida (208 mg, rendimiento 95%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de fenilacetilo (100 mL; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 1,98-2,26 (1H; m); 2,40 (3H; s); 2,50 (3H; s); 3,04 (2H; s); 3,40 (2H; s); 3,78 (2H; s); 6,94-6,97 (2H; m); 7,12-7,53 (7H; m); 8,44 (3H; brs); 9,90 (1H; brs).

Ejemplo 225

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-3-fenilpropanamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-3-fenilpropanamida (208 mg, rendimiento 92%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-

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APOSTILLE

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Tsutomu HIGUCHI

For the Minister for Foreign Affairs

il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de hidrocinnamoilo (111 mL; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,15-2,23 (1H; m); 2,33 (2H; t; J = 7,2 Hz); 2,37 (6H; s); 2,63 (2H; t; J = 7,2 Hz); 2,94 (2H; brs); 3,79 (2H; s); 7,10-7,29 (9H; m); 8,26 (3H; brs); 9,43 (1H; brs).

Ejemplo 226

Dihidrocloruro de (2E)-N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-3-fenilacrilamida

El dihidrocloruro de (2E)-N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-3-fenilacrilamida (208 mg; rendimiento 92%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de cinnamoilo (125 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,15-2,28 (1H; m); 2,34 (3H; s); 2,55 (3H; s); 3,02 (2H; brs); 3,83 (2H; brs); 6,63 (1H; d; J = 15,6 Hz); 7,16-7,23 (2H; m); 7,28-7,32 (2H; m); 7,39-7,46 (4H; m); 7,52-7,56 (2H; m); 8,36 (3H; brs), 9.76 (1H, brs).

Ejemplo 227

Dihidrocloruro de etil [({[5-(aminometil)-6-isobutil-2-metil-

4-(4-metilfenil)piridin-3-il]amino}carbonil)oxi]acetato

1) El etil [({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)oxi]acetato fue obtenido como un aceite de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y hidroxiacetato de etilo (104 mg; 2,0 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):514

2) Dihidrocloruro de etil [({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)oxi]acetato (202 mg, rendimiento 45%) fue obtenido como polvo blanco del aceite obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,96 (6H; d; J = 6,3 Hz); 1,18 (3H; t; J = 7,2 Hz); 2,11-2,29 (1H; m); 2,38 (3H; s); 2,86 (3H; s); 3,77 (2H; brs); 3,91 (2H; brs); 4,12 (2H; q; J = 7,2 Hz); 4,52 (2H; s); 7,15 (2H; d; J = 7,8 Hz); 7,29 (2H; d; J = 7,8 Hz); 8,21 (3H; brs), 9,12 (1H; brs).

Ejemplo 228

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-N'-bencilurea

1) Terc-butil {[5-{[(bencilamino)carbonil]amino}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato fue obtenido como un aceite de ácido 5-{[(terc-

butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y bencilamina (218 mL; 2,0 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):517

2) Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-N'-bencilurea (181 mg, rendimiento 40%) fue obtenido como polvo blanco del aceite obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,3 Hz); 2,09-2,22 (1H; m); 2,41 (3H; s); 2,50 (3H; s); 2,65 (2H; brs); 3,81 (2H; brs); 4,19(2H; brs); 7,11-7,35 (9H; m); 8,43 (3H; brs).

Ejemplo 229

Dihidrocloruro de metil 4-{[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)oxi]metil}benzoato

1) El metil 4-{[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)oxi]metil}benzoato fue obtenido como un aceite de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y 4-hidroximetilbenzoato de metilo (250 mg; 1,5 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):576

2) Dihidrocloruro de metil 4-{[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)oxi]metil}benzoato (195 mg, rendimiento 38%) fue obtenido como polvo blanco del aceite obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,97 (6H; d; J = 6,3 Hz); 2,14-2,23 (1H; m); 2,39 (3H; s); 2,55 (3H; s); 2,97 (2H; brs); 3,78 (2H; brs); 3,87 (3H; s); 5,09 (2H; brs); 7,14-7,29 (6H; m); 7,92 (2H; d; J = 8,4 Hz); 8,30 (3H; brs); 9,19 (1H; brs).

Ejemplo 230

Dihidrocloruro de ácido 3-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]benzoico

1) A una solución de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,70 g; 4,12 mmol) en N,N-dimetilformamida (15 mL) fue agregado metil 3-(bromometil)benzoato (0,79 g; 3,43 mmol) y carbonato de potasio (0,71 g; 5,15 mmol) y la mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue diluida con acetato de etilo, y la mezcla fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por

cromatografía en columna de gel de sílice para dar 3-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,80 g; rendimiento 94%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,16-2,25 (1H; m); 2,33 (3H; s); 2,53 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,94 (3H; s); 4,13 (2H; brs); 4,20 (1H; brs); 4,95 (2H; s); 7,01 (2H; d; J = 8,1 Hz); 7,09 (2H; d; J = 7,9 Hz); 7,22 (1H; d; J = 7,7 Hz); 7,35 (1H; t; J = 7,7 Hz); 7,83 (1H; s); 7,98 (1H; d; J = 7,7 Hz).

2) El ácido 3-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]benzoico (1,43 g; rendimiento 87%) fue obtenido como un aceite incoloro de 3-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,69 g; 3,01 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,13-2,25 (1H; m); 2,34 (3H; s); 2,55 (3H; s); 2,80 (2H; d; J = 7,4 Hz); 4,11-4,16 (2H; m); 4,22 (1H; brs); 4,98 (2H; s); 7,02 (2H; d; J = 7,9 Hz); 7,11 (2H; d; J = 7,7 Hz); 7,26-7,30 (1H; m); 7,39 (1H; t; J = 7,7 Hz); 7,89 (1H; s); 8,04 (1H; d; J = 7,5 Hz).

3) El dihidrocloruro de ácido 3-[({[5-(Aminometil)-6-

isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]benzoico (293 mg, rendimiento 60%) fue obtenido como un sólido blanco de ácido 3-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]benzoico (0.50 g; 0,927 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,16-2,25 (1H; m); 2,32 (3H; s); 2,54 (3H; s); 2,90 (2H; d; J = 6,6 Hz); 3,81 (2H; d; J = 5,1 Hz); 5,04 (2H; s); 7,13 (2H; d; J = 8,5 Hz); 7,17 (2H; d; J = 8,3 Hz); 7,26-7,30 (1H; m); 7,44 (1H; t; J = 7,6 Hz); 7,73-7,74 (1H; m); 7,89-7,92 (1H; m); 8,30 (3H; brs).

Ejemplo 231

Dihidrocloruro de ácido 2-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]benzoico

1) A una solución de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,10 g; 2,67 mmol) en N,N-dimetilformamida (15 mL) fue agregado bromuro de 2-bromobencilo (0,61 g; 2,43 mmol) y carbonato de potasio (0,51 g; 3,65 mmol) y la mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue diluída con acetato de etilo, fue lavada con solución salina saturada y

fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar 2-bromobencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,23 g; rendimiento 87%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,38 (9H; s); 2,14-2,25 (1H; m); 2,35 (3H; s); 2,56 (3H; s); 2,78 (2H; d; J = 7,2 Hz); 4,11-4,13 (2H; m); 4,22 (1H; brs); 5,05 (2H; s); 7,02-7,05 (3H; m); 7,11 (2H; d; J = 7,9 Hz); 7,16-7,21 (2H; m); 7,51-7,54 (1H; m).

2) El 2-Bromobencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,23 g; 2,12 mmol), trietilamina (0,59 mL; 4,24 mmol) y bicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio(II) (174 mg; 0,212 mmol) fue disuelto en metanol (5 mL) - N,N-dimetilformamida (15 mL) y la mezcla resultante fue agitada bajo atmósfera de monóxido de carbono por 14 hrs. La mezcla de reacción fue diluída con acetato de etilo (100 mL) y la mezcla fue lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar 2-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,88 g;

rendimiento 74%) fue obtenido como un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,16-2,25 (1H; m); 2,35 (3H; s); 2,56 (3H; s); 2,78 (2H; d; J = 7,2 Hz); 3,87 (3H; s); 4,11-4,16 (2H; m); 4,21 (1H; brs); 5,39 (2H; s); 7,01-7,06 (3H; m); 7,11 (2H; d; J = 7,9 Hz); 7,32-7,42 (2H; m); 7,93-7,96 (1H; m).

3) El ácido 2-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]benzoico (0,75 g; rendimiento 89%) fue obtenido como un aceite incoloro de 2-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,88 g; 1,54 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,37 (9H; s); 2,12-2,21 (1H; m); 2,36 (3H; s); 2,54 (3H; s); 2,83 (2H; d; J = 7,2 Hz); 4,13-4,18 (2H; m); 4,25 (1H; brs); 5,38 (2H; s); 7,01-7,04 (3H; m); 7,11 (2H; d; J = 7,5 Hz); 7,38-7,46 (2H; m); 8,06-8,09 (1H, m).

4) El dihidrocloruro de ácido 2-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]benzoico (278 mg, rendimiento 65%) fue obtenido como un sólido blanco de ácido 2-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]benzoico (0,45 g;

0,823 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,18-2,27 (1H; m); 2,35 (3H; s); 2,84 (2H; d; J = 7,2 Hz); 3,82 (2H; d; J = 5,3 Hz); 5,32 (2H; s); 6,97-7,00 (1H; m); 7,18 (2H; d; J = 8,3 Hz); 7,24 (2H; d; J = 7,9 Hz); 7,41-7,51 (2H; m); 7,87-7,91 (1H; m); 8,19 (3H; brs).

Ejemplo 232

Dihidrocloruro de metil 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoato

Dihidrocloruro de Metil 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoato (230 mg, rendimiento 89%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de éster monometil ácido tereftálico (149 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,22-2,31 (1H; m); 2,31 (3H; s); 2,54 (3H; s); 2,95 (2H; brs); 3,85 (2H; brs); 3,87 (3H; s); 7,20-7,27 (4H; m); 7,72 (2H; d; J = 8,4 Hz); 7,99 (2H; d; J = 8,4 Hz); 8,26 (3H; brs); 10,13 (1H; brs).

Ejemplo 233

Dihidrocloruro de ácido 4-({[5-(aminometil)-6-isobutil-2-

metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoico

1) El ácido 4-({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoico (248 mg, rendimiento 98%) fue obtenido como polvo blanco de metil 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoato (260 mg; 0,48 mmol) según un método similar al método del Ejemplo 36-1).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 1,35 (9H; s); 2,18-2,29 (1H; m); 2,29 (3H; s); 2,59 (3H; s); 2,88 (2H; brs); 3,99 (2H; brs); 7,14 (1H; s); 7,20 (4H; s); 7,70 (2H; d; J = 8,4 Hz); 7,97 (2H; d; J = 8,4 Hz); 10,13 (1H; brs).

2) El dihidrocloruro de ácido 4-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoico (230 mg, rendimiento 99%) fue obtenido como polvo blanco de ácido 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoico (248 mg; 0,47 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,22-2,32 (1H; m); 2,31 (3H; s); 2,55 (3H; s); 2,96 (2H; brs); 3,83 (2H; brs); 7,20-7,27 (4H; m); 7,70 (2H; d; J = 8,1 Hz); 7,96 (2H; d; J = 8,1 Hz); 8,26 (3H; brs); 10,11 (1H; brs).

Ejemplo 234

Dihidrocloruro de metil (4-{[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}fenil)acetato

1) metil (4-{[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}fenil)acetato (0,36 g; rendimiento 61%) fue obtenido como polvo blanco de terc-butil {[5-(hidroximetil)-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (0,44 g; 1,1 mmol) y metil 4-hidroxifenilacetato (0,18 g; 1,1 mmol) según un método similar al método del Ejemplo 214-1).

^{1}H-RMN ($CDCl_3$)δ: 1,03 (9H; s); 1,37 (9H; s); 2,36 (3H; s); 2,61 (3H; s); 2,87 (2H; s); 3,55 (2H; s); 3,68 (3H; s); 4,05-4,25 (3H; m); 4,59 (2H; s); 6,76 (2H; d; J = 8,5 Hz); 7,05 (2H; d; J = 8,5 Hz); 7,14 (2H; d; J = 8,5 Hz); 7,17 (2H; d; J = 8,5 Hz).

2) El dihidrocloruro de metil (4-{[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}fenil)acetato (0,088 g; rendimiento 74%) fue obtenido como polvo blanco de metil (4-{[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}fenil)acetato (0,13 g; 0,22 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ: 1,04 (9H; s); 2,35 (3H; s); 2,77 (3H; brs); 3,14 (2H; brs); 3,58 (2H; d; J = 7,0 Hz); 3,59 (3H; s); 3,87

(2H; s); 4,66 (2H; s); 6,80 (2H; d; J = 8,7 Hz); 7,14 (2H; d; J = 8,7 Hz); 7,25 (2H; d; J = 7,7 Hz); 7,31 (2H; d; J = 7,7 Hz); 8,20 (3H, brs).

Ejemplo 235

Dihidrocloruro de metil 2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-1,3-oxazol-4-carboxilato

1) El metil N-{[5-ciano-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}serinato (5,37 g; rendimiento 87%) fue obtenido como un aceite incoloro de ácido 5-ciano-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (5,00 g; 11,2 mmol) y serine metilo éster hidrocloruro de(2,09 g; 13,4 mmol) según un método similar al método del Ejemplo 195-2),

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d, J = 5,7 Hz); 2,15-2,26 (1H; m); 2,38 (3H; s); 2,57 (3H; s); 2,80 (2H; d; J = 7,0 Hz); 3,36-3,42 (1H; m); 3,61-3,69 (1H; m); 3,73 (3H; s); 4,19-4,29 (2H; m); 4,43-4,52 (2H; m); 5,03 (2H; s); 6,21 (1H; d; J = 7,0 Hz); 7,12-7,17 (2H; m); 7,17-7,22 (2H; m); 7,29-7,38 (5H; m).

2) Una solución de metil N-{[5-ciano-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}serinato (5,37 g; 9,81 mmol) en diclorometano (50 mL) fue enfriada a -78°C y fue agregado trifluoruro de dietilaminosulfuro (1,72 mL; 11,8 mmol). La mezcla fue agitada a la misma temperatura por 1 hr. El carbonato de potasio (1,36 g; 14,7 mmol) fue agregado y la mezcla fue agitada a la temperatura ambiente por 30 min.

La mezcla de reacción fue diluída con acetato de etilo, fue lavada con carbonato hidrógeno de sodio acuoso saturado y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar metil 2-[5-ciano-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4,5-dihidro-1,3-oxazol-4-carboxilato (3,59 g; rendimiento 69%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,95 (6H; d; J = 6,6 Hz); 2,15-2,26 (1H; m); 2,37 (3H; s); 2,57 (3H; s); 2,81 (2H; d; J = 7,2 Hz); 3,71 (3H; s); 4,11-4,16 (1H; m); 4,23 (2H; d; J = 5,5 Hz); 4,33 (1H; dd; J = 8,8; 7,4 Hz); 4,59-4,65 (1H; m); 5,03 (2H; s); 7,05 (2H; d; J = 8,5 Hz); 7,13-7,21 (2H; m); 7,29-7,38 (5H; m).

3) Una solución de metil 2-[5-ciano-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4;5-dihidro-1,3-oxazol-4-carboxilato (0,83 g; 2,12 mmol) y 1,8-diazabiciclo[5,4,0]-7-undeceno (1,11 mL; 7,42 mmol) en diclorometano (10 mL) fue enfriada a 0°C y fue agregado bromotriclorometano (0,73 mL; 7,42 mmol). La mezcla fue agitada a la misma temperatura por 1 hr. La mezcla de reacción fue diluída con acetato de etilo, fue lavada con solución de cloruro de amonio acuosa saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para

dar metil 2-[5-ciano-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-1,3-oxazol-4-carboxilato (520 mg, rendimiento 63%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:1,03 (6H; d; J = 6,8 Hz); 2,24-2,34 (4H; m); 2,59 (3H; s); 3,00 (2H; d; J = 7,4 Hz); 3,92 (3H; s); 7,11 (2H; d; J = 8,5 Hz); 7,16 (2H; d; J = 8,3 Hz); 8,08 (1H; s).

4) El dihidrocloruro de metil 2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-1,3-oxazol-4-carboxilato (456 mg, rendimiento 73%) fue obtenido como un sólido blanco de metil 2-[5-ciano-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-1,3-oxazol-4-carboxilato (0,52 g; 1,34 mmol) según un método similar al método del Ejemplo 108-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,21-2,30 (4H; m); 2,45-2,48 (3H; m); 2,90-3,02 (2H; m); 3,78 (3H; s); 3,85 (2H; d; J = 4,7 Hz); 7,11 (2H; dd; J = 8,1; 2,1 Hz); 7,20 (2H; d; J = 8,1 Hz); 8,30-8,47 (3H; m); 8,77 (1H; d; J = 1,5 Hz).

Ejemplo 236

Dihidrocloruro de 2-(4-{[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}fenil)acetamida

1) Terc-butil {[5-{[4-(2-amino-2-oxoetil)fenoxi]metil}-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (0,14 g; rendimiento 47%) fue obtenido

como polvo blanco de terc-butil {[5-(hidroximetil)-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (0,22 g; 0,53 mmol) y 4-hidroxifenilacetamida (0,081 g; 0,53 mmol) según un método similar al método del Ejemplo 214-1).

^{1}H-RMN ($CDCl_3$)δ: 1,04 (9H; s); 1,37 (9H; s); 2,36 (3H; s); 2,62 (3H; s); 2,88 (2H; s); 3,51 (2H; s); 4,10-4,25 (3H; m); 4,61 (2H; s); 5,35 (2H; brs); 6,75-6,80 (2H; m); 7,05 (2H; d; J = 7,9 Hz); 7,10-7,20 (4H; m).

2) El dihidrocloruro de 2-(4-{[5-(Aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}fenil)acetamida (0,098 g; rendimiento 92%) fue obtenido como polvo amarillo pálido de terc-butil {[5-{[4-(2-amino-2-oxoetil)fenoxi]metil}-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (0,11 g; 0,20 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ: 1,05 (9H; s); 2,36 (3H; s); 2,79 (3H; brs); 3,05-3,25 (2H; m); 3,28 (2H; s); 3,88 (2H; brs); 4,66 (2H; s); 6,79 (2H; d; J = 8,5 Hz); 6,83 (1H; brs); 7,14 (2H; d; J = 8,5 Hz); 7,26 (2H; d; J = 7,4 Hz); 7,33 (2H; d; J = 7,4 Hz); 7,42 (1H; brs); 8,19 (3H; brs).

Ejemplo 237

metil (4-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}fenil)acetato

1) El metil (4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-

isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}fenil)acetato (570 mg, rendimiento 83%) fue obtenido como un aceite incoloro del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (500 mg; 1,25 mmol) y metil (4-hidroxifenil)acetato (250 mg; 1,51 mmol) según un método similar al método del Ejemplo 214-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,17-2,30 (1H; m); 2,36 (3H; s); 2,62 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 3,51 (2H; s); 3,56 (3H; s); 4,10 (2H; d; J = 4,7 Hz); 4,20 (1H; s); 4,61 (2H; s); 6,78 (2H; d; J = 8,5 Hz); 7,06 (2H; d; J = 8,5 Hz); 7,12-7,20 (4H; m).

2) El metil (4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}fenil)acetato (570 mg; 1,04 mmol) fue disuelto en ácido trifluoracético (10 mL) y la mezcla fue agitada por 1 hr. La mezcla de reacción fue concentrada bajo presión reducida y el residuo fue dividido entre acetato de etilo y carbonato hidrógeno de sodio acuoso saturado. La capa orgánica fue secada sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice para dar metil (4-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}fenil)acetato (300 mg, rendimiento 65%) como un aceite incoloro.

^{1}H-RMN (DMSO-d_6)δ:0,98 (6H; d; J = 6,6 Hz); 2,18-2,25 (1H; m); 2,34 (3H; s); 2,60 (3H; s); 2,88 (2H; d; J = 7,4 Hz); 3,30 (2H; d; J = 5,3 Hz); 3,61 (3H; s); 4,20 (2H; d; J = 4,7 Hz); 4,60 (2H; s);6,70 (2H; d; J = 8,5 Hz); 6,79 (2H; d; J = 8,5 Hz); 7,05 (2H; d; J = 8,3 Hz); 7,15 (2H; d; J = 8,3 Hz).

Ejemplo 238

Dihidrocloruro de ácido 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoico

El dihidrocloruro de ácido 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoico (230 mg, rendimiento 89%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de éster monometil ácido isoftálico (149 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:1,01 (6H; d; J = 6,6 Hz); 2,18-2,31 (1H; m); 2,31 (3H; s); 2,60 (3H; s); 3,04 (2H; brs); 3,85 (2H; brs); 7,25 (4H; s); 7,57 (1H; t; J = 7,8 Hz); 7,86 (1H; d; J = 7,8 Hz); 8,07 (1H; d; J = 7,8 Hz); 8,16 (1H; s); 8,36 (3H; brs); 10,19 (1H, brs).

Ejemplo 239

Metil 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1H-indol-2-carboxilato

1) El metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1H-indol-2-carboxilato (0,41 g; rendimiento 52%) fue obtenido como un sólido amarillo pálido del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,60 g; 1,49 mmol) y metil 3-hidroxiindol-2-carboxilato (0,26 g; 1,36 mmol) según un método similar al método del Ejemplo 214-1),

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,37 (9H; s); 2,17-2,26 (1H; m); 2,37 (3H; s); 2,77 (2H; d; J = 7,2 Hz); 2,86 (3H; s); 3,82 (3H; s); 4,00 (2H; d; J = 4,5 Hz); 4,09 (1H; brs); 5,03 (2H; s); 6,74-6,89 (4H; m); 7,09 (2H; d; J = 7,9 Hz); 7,21-7,31 (2H; m); 8,28 (1H; brs).

2) El metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1H-indol-2-carboxilato (0,26 g; 1,36 mmol) fue disuelto en solución 4N ácido clorhídrico acetato de etilo (10 mL) y la mezcla fue agitada a la temperatura ambiente por 30 min. La mezcla de reacción fue neutralizada con carbonato hidrógeno de sodio acuoso saturado y fue extraída con acetato de etilo. El extracto fue secado sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida. El sólido amarillo obtenido fue recristalizado del acetato de etilo - hexano para dar metil 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1H-indol-2-carboxilato

(256 mg, rendimiento 75%) como cristales amarillo pálidos. ^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 2,17-2,30 (1H; m); 2,38 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 2,86 (3H; s); 3,51 (2H; s); 3,83 (3H; s); 5,02 (2H; s); 6,77-6,88 (4H; m); 7,10 (2H; d; J = 7,7 Hz); 7,22-7,28 (2H; m); 8,27 (1H; brs).

Ejemplo 240

4-cianobencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) El 4-cianobencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2,32 g; rendimiento 86%) fue obtenido como un aceite amarillo de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (2,10 g; 5,10 mmol) y 4-cianobencil bromuro (1,00 g; 5,10 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,38 (9H; s); 2,17-2,26 (1H; m); 2,37 (3H; s); 2,54 (3H; s); 2,78 (2H; d; J = 7,2 Hz); 4,11-4,13 (2H; m); 4,20 (1H; brs); 4,98 (2H; s); 7,01 (2H; d; J = 8,1 Hz); 7,10 (4H; d; J = 8,1 Hz); 7,54 (2H; d; J = 8,3 Hz).

2) 4-cianobencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,52 g; 0,985 mmol) fue disuelto en el ácido trifluoracético (10 mL) y la mezcla fue agitada a la temperatura ambiente por 1 hr. La

mezcla de reacción fue neutralizada con carbonato hidrógeno de sodio acuoso saturado y se extrajo dos veces con acetato de etilo. El extracto fue secado sobre sulfato de magnesio anhidro dar 4-cianobencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,42 g; rendimiento 99%) como un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ:0,90 (6H; d; J = 6,6 Hz); 2,08-2,17 (1H; m); 2,32 (3H; s); 2,54 (3H; s); 2,70 (2H; d; J = 7,0 Hz); 3,97 (2H; s); 4,99 (2H; s); 7,00 (2H; d; J = 8,1 Hz); 7,08-7,14 (4H; m); 7,54 (2H; d; J = 8,3 Hz).

Ejemplo 241

dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]quinoxalin-2-carboxamida

Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]quinoxalin-2-carboxamida (137 mg, rendimiento 50%) fue obtenido como polvo blanco de terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de quinoxalina-2-carbonilo (144 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:1,02 (6H; d; J = 6,6 Hz); 2,22-2,29 (1H; m); 2,23 (3H; s); 2,64 (3H; s); 3,06 (2H; brs); 3,86 (2H; brs); 7,22 (2H; d; J = 8,1 Hz); 7,29 (2H; d; J = 8,1 Hz); 7,96-8,04 (2H; m); 8,11-8,28 (2H; m); 8,39 (3H; brs); 9,34

(1H; s); 10,50 (1H; brs).

Ejemplo 242

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2,5-dimetilfuran-3-carboxamida

N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2,5-dimetilfuran-3-carboxamida dihidrocloruro de (215 mg, rendimiento 90%) fue obtenido como polvo blanco de terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro del 2,5-dimetilfuran-3-carbonilo (119 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,17 (3H; s); 2,17-2,29 (1H; m); 2,29 (3H; s); 2,34 (3H; s); 2,54 (3H; s); 2,99 (2H; brs); 3,82 (2H; d; J = 5,1 Hz); 6,25 (1H; s); 7,20 (2H; d; J = 8,1 Hz); 7,26 (2H; d; J = 8,1 Hz); 8,28 (3H; brs); 9,32 (1H; brs).

Ejemplo 243

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-3-metiltiofen-2-carboxamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-3-metiltiofen-2-carboxamida (215 mg, rendimiento 90%) fue obtenido como polvo blanco de terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro del 3-metiltiofen-2-carbonilo (120 mg; 0,75 mmol)

según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,08 (3H; s); 2,09-2,33 (1H; m); 2,34 (3H; s); 2,51 (3H; s); 2,91 (2H; brs); 3,82 (2H; brs); 6,89 (1H; d; J = 5,1 Hz); 7,19 (2H; d; J = 7,8 Hz); 7,27 (2H; d; J = 7,8 Hz); 7,55 (1H; d; J = 5,1 Hz); 8,17 (3H; brs); 9,37 (1H; brs).

Ejemplo 244

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-1-benzotiofen-2-carboxamida

Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-1-benzotiofen-2-carboxamida (215 mg, rendimiento 90%) fue obtenido como polvo blanco de terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de 1-benzotiofen-2-carbonilo (150 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,20-2,28 (1H; m); 2,28 (3H; s); 2,60 (3H; s); 3,00 (2H; brs); 3,84 (2H; d; J = 5,4 Hz); 7,25 (4H; s); 7,41-7,50 (2H; m); 7,91 (1H; d; J = 6,9 Hz); 8,00 (1H; d; J = 6,9 Hz); 8,04 (1H; s); 8,33 (3H; brs); 10,34 (1H; brs).

Ejemplo 245

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-3-metil-1-benzofuran-2-carboxamida

Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-3-metil-1-benzofuran-2-carboxamida (213 mg, rendimiento 90%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de 3-metil-1-benzofuran-2-carbonilo (150 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,16-2,29 (1H; m); 2,29 (3H; s); 2,41 (3H; s); 2,60 (3H; s); 3,03 (2H; brs); 3,83 (2H; brs); 7,25 (4H; s); 7,35 (1H; t; J = 6,9 Hz); 7,49 (1H; t; J = 6,9 Hz); 7,56 (1H; d; J = 6,9 Hz); 7,73 (1H; d; J = 6,9 Hz); 8,35 (3H; brs), 10,08 (1H, brs).

Ejemplo 246

Dihidrocloruro de metil [4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)-2-oxopiperazin-1-il]acetato

1) Metil [4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)-2-oxopiperazin-1-il]acetato fue obtenido como un aceite de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y metil (2-oxopiperazin-1-il)acetato (344 mg; 2,0 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):582

2) Dihidrocloruro de metil [4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)-2-oxopiperazin-1-il]acetato (271 mg, rendimiento 49%) fue obtenido como polvo blanco del aceite obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,98 (6H; d; J = 6,3 Hz); 1,99-2,28 (1H; m); 2,37 (3H; s); 2,50 (3H; s); 2,60 (2H; brs); 3,14 (2H; t; J = 5,1 Hz); 3,46 (2H; t; J = 5,1 Hz); 3,66 (3H; s); 3,81 (4H; brs); 4,08 (2H; s); 7,17 (2H; d; J = 7,8 Hz); 7,29 (2H; d; J = 7,8 Hz); 8,43 (3H; brs).

Ejemplo 247

[5-(metoxicarbonil)piridin-2-il]metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) A una solución de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,85 g; 4,48 mmol), metil 6-(hidroximetil)nicotinato (0,68 g; 4,07 mmol) y trifenilfosfina (1,39 g; 5,29 mmol) en tetrahidrofurano (20 mL) fue agregado solución 40% dietil azodicarboxilato tolueno (2,3 mL; 5,29 mmol) y la mezcla fue agitada a la temperatura ambiente por 30 min. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar [5-(metoxicarbonil)piridin-2-il]metil 5-{[(terc-

butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2,29 g; rendimiento 99%) como un sólido blanco.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,17-2,26 (1H; m); 2,35 (3H; s); 2,58 (3H; s); 2,79 (2H; d; J = 7,2 Hz); 3,96 (3H; s); 4,13-4,15 (2H; m); 4,21 (1H; brs); 5,11 (2H; s); 6,88 (1H; d; J = 8,5 Hz); 7,06 (2H; d; J = 8,1 Hz); 7,13 (2H; d; J = 7,9 Hz); 8,14 (1H; dd; J = 8,2; 2,2 Hz); 9,10 (1H; dd; J = 2,1; 0,75 Hz).

2) [5-(Metoxicarbonil)piridin-2-il]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,37 g; 0,659 mmol) fue disuelto en solución 4N ácido clorhídrico acetato de etilo (10 mL) y la mezcla fue agitada a la temperatura ambiente por 30 min. La mezcla de reacción fue neutralizada con carbonato hidrógeno de sodio acuoso saturado y fue extraída con acetato de etilo. El extracto fue secado sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida para dar [5-(metoxicarbonil)piridin-2-il]metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (142 mg, rendimiento 46%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 2,17-2,29 (1H; m); 2,35 (3H; s); 2,57 (3H; s); 2,81 (2H; d; J = 7,4 Hz); 3,65 (2H; s); 3,96 (3H; s); 5,11 (2H; s); 6,89 (1H; d; J = 8,3

Hz); 7,10-7,16 (4H; m); 8,14 (1H; dd; J = 8,2; 2,2 Hz); 9,10 (1H; d; J = 1,3 Hz).

Ejemplo 248

Trihidrocloruro de ácido 6-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]nicotinico

1) El ácido 6-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]nicotinico (1,08 g; rendimiento 58%) fue obtenido como un aceite incoloro de [5-(metoxicarbonil)piridin-2-il]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,90 g; 3,38 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,27-2,35 (4H; m); 2,60 (3H; s); 2,81 (2H; d; J = 7,2 Hz); 4,14-4,15 (2H; m); 4,25 (1H; brs); 5,14 (2H; s); 6,88-6,95 (1H; m); 7,06-7,19 (4H; m); 8,19 (1H; dd; J = 8,2; 2,2 Hz); 9,16 (1H, s).

2) El trihidrocloruro de ácido 6-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]nicotinic (413 mg, rendimiento 81%) fue obtenido como un sólido blanco de ácido 6-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]nicotinico (0.50

g; 0.913 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,18-2,28 (1H; m); 2,33 (3H; s); 2,63 (3H; brs); 2,90-2,97 (2H; m); 3,82 (2H; d; J = 5,1 Hz); 5,15 (2H; s); 7,03 (1H; d; J = 8,1 Hz); 7,17-7,23 (4H; m); 8,17 (1H; dd; J = 8,2; 2,0 Hz); 8,38 (3H; brs); 8,98 (1H; d; J = 1,5 Hz).

Ejemplo 249

[5-(aminocarbonil)piridin-2-il]metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) El [5-(Aminocarbonil)piridin-2-il]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (222 mg, rendimiento 38%) fue obtenido como un aceite incoloro de ácido 6-[({[5-({[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]nicotinico (0,58 g; 1,06 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,17-2,26 (1H; m); 2,36 (3H; s); 2,58 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 4,13-4,15 (2H; m); 4,22 (1H; brs); 5,10 (2H; s); 6,92 (1H; d; J = 7,9 Hz); 7,07 (2H; d; J = 8,1 Hz); 7,14 (2H; d; J = 7,9 Hz); 8,03 (1H; dd; J = 8,3; 2,3 Hz); 8,89 (1H; d; J = 2,3 Hz).

2) El [5-(Aminocarbonil)piridin-2-il]metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (159 mg; rendimiento 87%) fue obtenido como un aceite incoloro de [5-(aminocarbonil)piridin-2-il]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,22 g; 0,406 mmol) según un método similar al método del Ejemplo 247-2).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 2,15-2,31 (1H; m); 2,36 (3H; s); 2,57 (3H; s); 2,81 (2H; d; J = 7,4 Hz); 3,65 (2H; s); 5,10 (2H; s); 6,94 (1H; d; J = 7,7 Hz); 7,11-7,17 (4H; m); 8,03 (1H; dd; J = 8,1; 2,3 Hz); 8,89 (1H; d; J = 2,3 Hz).

Ejemplo 250

Tetrahidrocloruro de Etil 4-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-etilpirimidin-5-carboxilato

1) El etil 4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-etilpirimidin-5-carboxilato (308 mg, rendimiento 40%) fue obtenido como un sólido blanco del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,53 g; 1,33 mmol) y etilo 2-etil-4-hidroxipirimidin-5-carboxilato (0,26 g; 1,33 mmol) según un método similar al método del Ejemplo 214-1),

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,8 Hz); 1,20-1,29 (6H; m);

1,39 (9H; s); 2,19-2,28 (1H; m); 2,34 (3H; s); 2,67 (3H; s); 2,75-2,83 (4H; m); 4,10 (2H; d; J = 4,9 Hz); 4,27-4,34 (3H; m); 5,22 (2H; s); 7,06 (2H; d; J = 8,1 Hz); 7,14 (2H; d; J = 7,9 Hz); 8,86 (1H; s).

2) El tetrahidrocloruro de etilo 4-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-etilpirimidin-5-carboxilato (269 mg, rendimiento 80%) fue obtenido como un sólido blanco del etil 4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-etilpirimidin-5-carboxilato (308 mg; 0,536 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 1,19 (3H; t; J = 7,5 Hz); 1,25 (3H; t; J = 7,1 Hz); 2,14-2,23 (1H; m); 2,43 (3H; s); 2,58-2,67 (2H; m); 2,81-2,97 (3H; m); 3,13 (2H; brs); 3,73-3,83 (2H; m); 4,22 (2H; t; J = 7,0 Hz); 4,42 (2H; s); 7,25-7,31 (2H; m); 7,38-7,43 (2H; m); 8,43 (3H; brs); 8,46 (1H; s).

Ejemplo 251

Dihidrocloruro de 4-(1H-tetrazol-5-il)bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) Una solución de 4-cianobencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,28 g; 2,43 mmol) y azida de tributilestaño (2,3 mL; 8,49 mmol) en tolueno (7,5 mL) fue

calentada bajo reflujo bajo una atmósfera de argón por 3 hrs. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar 4-(1H-tetrazol-5-il)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,23 g; rendimiento 88%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,15-2,24 (1H; m); 2,25 (3H; s); 2,54 (3H; s); 2,83 (2H; d; J = 7,2 Hz); 4,18 (2H; d; J = 4,9 Hz); 4,32 (1H; brs); 5,00 (2H; s); 7,01 (2H; d; J = 7,9 Hz); 7,07 (2H; d; J = 7,9 Hz); 7,18 (2H; d; J = 8,1 Hz); 8,03 (2H; d; J = 8,1 Hz).

2) Dihidrocloruro de 4-(1H-Tetrazol-5-il)bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (688 mg, rendimiento 95%) fue obtenido como un sólido blanco de 4-(1H-tetrazol-5-il)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,75 g; 1,33 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,17-2,26 (1H; m); 2,30 (3H; s); 2,54 (3H; s); 2,87 (2H; d; J = 6,8 Hz); 3,81 (2H; d; J = 5,5 Hz); 5,08 (2H; s); 7,14-7,25 (6H; m); 8,02 (2H; d; J = 8,1 Hz); 8,22 (3H; brs).

Ejemplo 252

Dihidrocloruro de ácido 5-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]furan-2-carboxílico

1) [5-(Metoxicarbonil)-2-furil]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2,37 g; rendimiento 88%) fue obtenido como un aceite amarillo de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (2,00 g; 4,85 mmol) y metil 5-(clorometil)furan-2-carboxilato (0,85 g; 4,85 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,13-2,24 (1H; m); 2,35 (3H; s); 2,52 (3H; s); 2,77 (2H; d; J = 7,2 Hz); 3,91 (3H; s); 4,11 (2H; d; J = 5,1 Hz); 4,19 (1H; brs); 4,94 (2H; s); 6,24 (1H; d; J = 3,6 Hz); 7,00 (2H; d; J = 8,1 Hz); 7,06 (1H; d; J = 3,6 Hz); 7,11 (2H; d; J = 7,9 Hz).

2) El ácido 5-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]furan-2-carboxílico (1,95 g; rendimiento 95%) fue obtenido como un sólido blanco de [5-(metoxicarbonil)-2-furil]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2,11 g; 3,83 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,14-2,25 (1H; m); 2,36 (3H; s); 2,53 (3H; s); 2,86 (2H; d; J = 7,0 Hz); 4,09-4,18 (2H; m); 4,26 (1H; brs); 4,99 (2H; s); 6,32 (1H; d; J = 3,4 Hz); 7,03 (2H; d; J = 8,1 Hz); 7,10-7,18 (3H, m).

3) Dihidrocloruro de ácido 5-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]furan-2-carboxílico (460 mg, rendimiento 79%) fue obtenido como un sólido blanco de ácido 5-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]furan-2-carboxílico (0,61 g; 1,14 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,16-2,27 (1H; m); 2,33 (3H; s); 2,90 (2H; brs); 3,80 (2H; d; J = 5,3 Hz); 5,05 (2H; s); 6,46 (1H; d; J = 3,4 Hz); 7,11-7,14 (3H; m); 7,17 (2H; d; J = 8,1 Hz); 8,29 (3H; brs).

Ejemplo 253

dihidrocloruro de [5-(aminocarbonil)-2-furil]metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) El [5-(Aminocarbonil)-2-furil]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (520 mg, rendimiento 69%) fue obtenido como un aceite incoloro del ácido 5-[({[5-{[(terc-

butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-furano-2-carboxílico (0,75 g; 1,40 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,14-2,27 (1H; m); 2,35 (3H; s); 2,52 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 4,06-4,13 (2H; m); 4,19 (1H; brs); 4,94 (2H; s); 5,45 (1H; brs); 6,16 (1H; brs); 6,27 (1H; d; J = 3,4 Hz); 6,98 (2H; d; J = 8,1 Hz); 7,04 (1H; d; J = 3,6 Hz); 7,09 (2H; d; J = 7,9 Hz).

2) Dihidrocloruro de [5-(Aminocarbonil)-2-furil]metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (471 mg, rendimiento 95%) fue obtenido como un sólido blanco de [5-(aminocarbonil)-2-furil]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,52 g; 0,971 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,14-2,27 (1H; m); 2,34 (3H; s); 2,88 (2H; brs); 3,80 (2H; d; J = 5,5 Hz); 5,02 (2H; s); 6,39 (2H; d; J = 3,4 Hz); 7,06 (1H; d; J = 3,4 Hz); 7,12 (2H; d; J = 7,9 Hz); 7,18 (2H; d; J = 8,3 Hz); 7,43 (1H; brs); 7,73 (1H; brs); 8,28 (3H; brs).

Ejemplo 254

dihidrocloruro de metil 3-{[[5-(aminometil)-6-isobutil-2-

metil-4-(4-metilfenil)piridin-3-il](metil)amino]carbonil}benzoato

A una mezcla de ácido 3-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoico (212 mg; 0,4 mmol), carbonato de potasio (138 mg; 1,0 mmol) y N,N-dimetilformamida (5 mL) fue agregado ioduro de metilo (282 mg; 2,0 mmol) y la mezcla fue agitada a la temperatura ambiente por 8 hrs. Fue agregado agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar un aceite. A una solución del aceite obtenido en el acetato de etilo (1 mL) fue agregado una solución 4N ácido clorhídrico acetato de etilo (1 mL) y la mezcla fue agitada a la temperatura ambiente por 1 hr. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue cristalizado del hexano para dar dihidrocloruro de metil 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il](metil)amino]carbonil}benzoato (203 mg, rendimiento 95%) como un polvo blanco.

EIMS(M+1):460

Ejemplo 255

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]isoftalamida

1) Terc-butil {[5-{[3-(aminocarbonil)benzoil]amino}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (248 mg, rendimiento 98%) fue obtenido como polvo blanco de 3-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoico el ácido (260 mg; 0,48 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,20-2,31 (1H; m); 2,33 (3H; s); 2,49 (3H; s); 2,78 (2H; brs); 4,13 (2H; brs); 4,40 (1H; brs); 5,79 (1H; brs); 6,38 (1H; brs); 7,03 (2H; d; J = 8,1 Hz); 7,18 (2H; d; J = 8,1 Hz); 7,39-7,45 (1H; brs); 7,60-7,63 (1H; m); 7,88-7,92 (2H; m).

2) Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]isoftalamida (233 mg, rendimiento 99%) fue obtenido como polvo blanco del terc-butil {[5-{[3-(aminocarbonil)benzoil]amino}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (248 mg; 0,47 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,3 Hz); 2,22-2,30 (1H; m); 2,30 (3H; s); 2,51 (3H; s); 2,89 (2H; brs); 3,84 (2H; brs); 7,23 (4H; s); 7,56 (1H; t; J = 7,8 Hz); 7,83 (2H; d; J

= 7,8 Hz); 8,06 (2H; d; J = 7,8 Hz); 8,14 (1H; s); 8,16 (3H; brs); 10,04 (1H; brs).

Ejemplo 256

Dihidrocloruro de 4-[2-oxo-2-(2-oxo-2-feniletoxi)etil]bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) 4-[2-Oxo-2-(2-oxo-2-feniletoxi)etil]bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2,85 g; rendimiento 86%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (2,00 g; 4,85 mmol) y fenacil 4-(bromometil)fenilacetato (1,69 g; 4,85 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,15-2,24 (1H; m); 2,38 (3H; s); 2,52 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,82 (2H; s); 4,11-4,16 (2H; m); 4,21 (1H; brs); 4,91 (2H; s); 5,36 (2H; s); 7,02-7,05 (4H; m); 7,15 (2H; d; J = 7,7 Hz); 7,26-7,29 (2H; m); 7,46-7,51 (2H; m); 7,58-7,64 (1H; m); 7,88-7,91 (2H; m).

2) Dihidrocloruro de 4-[2-Oxo-2-(2-oxo-2-feniletoxi)etil]bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (117 mg, rendimiento 45%) fue obtenido como un sólido blanco de 4-[2-oxo-2-(2-oxo-2-feniletoxi)etil]bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,27 g; 0,398

mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,16-2,27 (1H; m); 2,38 (3H; s); 2,83 (2H; brs); 3,81 (2H; d; J = 5,3 Hz); 3,85 (2H; s); 4,95 (2H; s); 5,53 (2H; s); 7,02 (2H; d; J = 8,1 Hz); 7,15 (2H; d; J = 7,5 Hz); 7,26 (4H; t; J = 7,72); 7,56 (2H; d; J = 7,9 Hz); 7,67-7,72 (1H; m); 7,92-7,98 (2H; m); 8,17 (3H; brs).

Ejemplo 257

Dihidrocloruro de 4-(2-metoxi-2-oxoetil)bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) El ácido {4-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]fenil}acético (1,65 g; rendimiento 77%) fue obtenido como un aceite incoloro de 4-[2-oxo-2-(2-oxo-2-feniletoxi)etil]bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (2,58 g; 3,80 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,95 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,14-2,23 (1H; m); 2,37 (3H; s); 2,52 (3H; s); 2,77 (2H; d; J = 7,2 Hz); 3,65 (2H; s); 4,09-4,16 (2H; m); 4,21 (1H; brs); 4,90 (2H; s); 7,00-7,06 (4H; m); 7,13 (2H; d; J = 7,9 Hz); 7,21 (2H; d; J = 8,1 Hz).

2) A una mezcla de ácido {4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-

metilfenil)piridin-3-il]carbonil}oxi)metil]fenil}acético (0.65 g; 1.16 mmol), carbonato de potasio (0,32 g; 2,32 mmol) y N,N-dimetilformamida (15 mL) fue agregado ioduro de metilo (197 mg; 1,39 mmol) y la mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue diluida con acetato de etilo, fue lavada con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar 4-(2-metoxi-2-oxoetil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,56 g; rendimiento 84%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,13-2,26 (1H; m); 2,38 (3H; s); 2,52 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,62 (2H; s); 3,70 (3H; s); 4,12-4,13 (2H; m); 4,20 (1H; brs); 4,90 (2H; s); 7,01-7,04 (4H; m); 7,14 (2H; d; J = 7,9 Hz); 7,20 (2H; d; J = 8,1 Hz).

3) El dihidrocloruro de 4-(2-metoxi-2-oxoetil)bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (483 mg, rendimiento 90%) fue obtenido como un sólido blanco de 4-(2-metoxi-2-oxoetil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,56 g; 0,974 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,95 (6H; d; J = 6,6 Hz); 2,14-2,26 (1H; m); 2,37 (3H; s); 2,79-2,88 (2H; m); 3,62 (3H; s); 3,69 (2H; s); 3,81 (2H; d; J = 5,3 Hz); 4,94 (2H; s); 7,00 (2H; d; J = 8,1 Hz); 7,13-7,24 (6H; m); 8,21 (3H; brs).

Ejemplo 258

Dihidrocloruro de ácido {4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]fenil}acético

Dihidrocloruro de ácido {4-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]fenil}acético (348 mg, rendimiento 73%) fue obtenido como un sólido blanco de ácido {4-[({[5-[[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]fenil}acético (0,50 g; 0,892 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,16-2,27 (1H; m); 2,37 (3H; s); 2,53 (3H; s); 2,90 (2H; d; J = 5,8 Hz); 3,57 (2H; s); 3,82 (2H; d; J = 5,3 Hz); 4,95 (2H; s); 6,99 (2H; d; J = 8,1 Hz); 7,15 (2H; d; J = 8,1 Hz); 7,20 (2H; d; J = 8,1 Hz); 7,23 (2H; d; J = 8,1 Hz); 8,30 (3H; brs).

Ejemplo 259

Dihidrocloruro de 4-(2-amino-2-oxoetil)bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) 4-(2-amino-2-oxoetil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (360 mg, rendimiento 72%) fue obtenido como un aceite incoloro de ácido {4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]fenil}acético (0,50 g; 0,892 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,95 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,13-2,26 (1H; m); 2,39 (3H; s); 2,52 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,58 (2H; s); 4,12-4,13 (2H; m); 4,21 (1H; brs); 4,91 (2H; s); 5,31 (2H; brs); 7,04-7,06 (4H; m); 7,16 (2H; d; J = 7,9 Hz), 7,20 (2H; d; J = 8,1 Hz).

2) Dihidrocloruro de 4-(2-amino-2-oxoetil)bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (231 mg, rendimiento 67%) fue obtenido como un sólido blanco de 4-(2-amino-2-oxoetil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,36 g; 0,643 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,95 (6H; d; J = 6,6 Hz); 2,14-2,25 (1H; m); 2,38 (3H; s); 2,86 (2H; brs); 3,37 (2H; s); 3,81 (2H; d; J = 5,5 Hz); 4,93 (2H; s); 6,88 (1H; brs); 6,98 (2H; d; J = 8,1 Hz); 7,13-7,25 (6H; m); 7,49 (1H; brs); 8,21 (3H; brs).

Ejemplo 260

Dihidrocloruro de 4-(metilsulfonil)bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) 4-(metilsulfonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (530 mg, rendimiento 73%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (495 mg; 1,20 mmol) y 1-(bromometil)-4-(metilsulfonil)benzene (300 mg; 1,20 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,19-2,28 (1H; m); 2,38 (3H; s); 2,55 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 3,04 (3H; s); 4,12-4,13 (2H; m); 4,21 (1H; brs); 5,01 (2H; s); 7,04 (2H; d; J = 8,1 Hz); 7,14 (2H; d; J = 7,9 Hz), 7,19 (2H; d; J = 8,3 Hz); 7,83 (2H; d; J = 8,5 Hz).

2) El dihidrocloruro de 4-(metilsulfonil)bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (466 mg, rendimiento 92%) fue obtenido como un sólido blanco de 4-(metilsulfonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,53 g; 0,913 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,15-2,26 (1H;

m); 2,36 (3H; s); 2,54-2,58 (3H; m); 2,87-2,97 (2H; m); 3,22 (3H; s); 3,81 (2H; d; J = 5,1 Hz); 5,11 (2H; s); 7,15-7,28 (6H; m); 7,84 (2H; d; J = 8,3 Hz); 8,23-8,40 (3H; m).

Ejemplo 261

Dihidrocloruro de etil 3-[4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)-2-oxopiperazin-1-il]propionato

1) El etil 3-[4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)-2-oxopiperazin-1-il]propionato fue obtenido como un aceite de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y etilo (2-oxopiperazin-1-il)propionate (250 mg; 2,0 mmol) según un método similar al método del Ejemplo 95-í).

EIMS(M+1):610

2) El dihidrocloruro de etil 3-[4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)-2-oxopiperazin-1-il]propionato (278 mg, rendimiento 49%) fue obtenido como polvo blanco del aceite obtenido en 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,3 Hz); 1,19 (3H; t; J = 7,2 Hz); 2,14-2,23 (1H; m); 2,37 (3H; s); 2,64 (2H; s); 3,06 (4H; brs); 3,37-3,47 (4H; m); 3,74 (2H; s); 3,83 (2H; brs);

4,06 (2H; q; J = 7,2 Hz); 7,18 (2H; d; J = 7,8 Hz); 7,29 (2H; d; J = 7,8 Hz); 8,40 (3H, brs).

Ejemplo 262

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2-metoxibenzamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2-metoxibenzamida (209 mg, rendimiento 95%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de 2-metoxibenzoilo (128 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,18-2,29 (1H; m); 2,36 (3H; s); 2,61 (3H; s); 3,03 (2H; s); 3,69 (3H; s); 3,84 (2H; brs); 6,98 (1H; t; J = 7,5 Hz); 7,08 (1H; d; J = 8,1 Hz); 7,24 (2H; d; J = 8,1 Hz); 7,32 (2H; d; J = 8,1 Hz); 7,39-7,49(2H; m); 8,32 (3H; brs); 9,55 (1H; brs).

Ejemplo 263

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2-fluorobenzamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2-fluorobenzamida (204 mg, rendimiento 95%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de 2-

fluorobenzoilo (122 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,21-2,28 (1H; m); 2,37 (3H; s); 2,55 (3H; s); 2,92 (2H; s); 3,84 (2H; s); 7,13-7,32 (7H; m); 7,49-7,54 (1H; m); 8,20 (3H; brs); 9,86 (1H; brs).

Ejemplo 264

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-3-metoxibenzamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-3-metoxibenzamida (196 mg, rendimiento 80%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de 3-metoxibenzoilo (128 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,19-2,31 (1H; m); 2,32 (3H; s); 2,58 (3H; s); 3,02 (2H; s); 3,75 (3H; s); 3,85 (2H; brs); 7,08-7,10 (2H; m); 7,18-7,36 (6H; m); 8,33 (3H; brs); 9,96 (1H; brs).

Ejemplo 265

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-3-fluorobenzamida

Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-

4-(4-metilfenil)piridin-3-il]-3-fluorobenzamida (186 mg, rendimiento 78%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de 3-fluorobenzoilo (122 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:1,01 (6H; d; J = 6,6 Hz); 2,18-2,36 (1H; m); 2,31 (3H; s); 2,62 (3H; s); 3,08 (2H; s); 3,86 (2H; s); 7,26 (4H; s); 7,38-7,42 (2H; m); 7,50 (2H; s); 8,41 (3H; brs); 10,22 (1H; brs).

Ejemplo 266

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-metoxibenzamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-metoxibenzamida (209 mg, rendimiento 95%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de 4-metoxibenzoilo (128 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,19-2,26 (1H; m); 2,31 (3H; s); 2,63 (3H; s); 3,12 (2H; s); 3,79 (3H; s); 3,87 (2H; brs); 6,96 (1H; t; J = 9,0 Hz); 7,25 (4H; s); 7,67 (2H; d; J = 9,0 Hz); 8,43 (3H; brs); 9,92 (1H; brs).

Ejemplo 267

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-fluorobenzamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-fluorobenzamida (204 mg, rendimiento 95%) fue obtenido como polvo blanco del terc-butil ([5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil)carbamato (192 mg; 0,5 mmol) y cloruro de 4-fluorobenzoilo (122 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,14-2,31 (1H; m); 2,31 (3H; s); 2,62 (3H; s); 3,08 (2H; s); 3,85 (2H; s); 7,25-7,30 (6H; m); 7,70-7,75 (2H; m); 8,41 (3H; brs); 10,14 (1H; brs).

Ejemplo 268

Dihidrocloruro de (5-metil-2-oxo-1,3-dioxol-4-il)metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato

1) El (5-metil-2-oxo-1,3-dioxol-4-il)metil [5-({[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (540 mg, rendimiento 86%) fue obtenido como polvo blanco de ácido [5-({[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acético (500 mg; 1,17 mmol) y 4-(clorometil)-5-metil-1,3-dioxol-2-ona (209 mg, 1.41 mmol)

según un método similar al método del Ejemplo 176-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,38 (9H; s); 2,14 (3H; s); 2,16-2,28 (1H; m); 2,40 (3H; s); 2,49 (3H; s); 2,75 (2H; d; J = 7,4 Hz); 3,40 (2H; s); 4,04 (2H; d; J = 5,1 Hz); 4,21 (1H; brs); 4,76 (2H; s); 6,93 (2H; d; J = 7,9 Hz); 7,21 (2H, d; J = 7,9 Hz).

2) El dihidrocloruro de (5-metil-2-oxo-1,3-dioxol-4-il)metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (500 mg, rendimiento 99%) fue obtenido como polvo blanco de (5-metil-2-oxo-1,3-dioxol-4-il)metil [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (530 mg; 0,984 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,15 (3H; s); 2,18-2,25 (1H; m); 2,39 (3H; s); 2,88 (3H; s); 3,29 (2H; d; J = 7,2 Hz); 3,54-3,64 (4H; m); 4,94 (2H; s); 7,16 (2H; d; J = 7,9 Hz); 7,33 (2H; d; J = 7,9 Hz); 8,63 (3H; brs).

Ejemplo 269

Dihidrocloruro de 2-[4-(metoxicarbonil)fenil]etil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) El 2-[4-(Metoxicarbonil)fenil]etil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,77 g; rendimiento 70%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-

butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,80 g; 4,37 mmol) y metilo 4-(2-bromoetil)benzoato (1,06 g; 4,37 mmol) según un método similar al método del Ejemplo 169-1),

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,16-2,28 (1H; m); 2,37 (3H; s); 2,46 (3H; s); 2,66 (2H; t; J = 7,0 Hz); 2,77 (2H; d; J = 7,4 Hz); 3,91 (3H; s); 4,11-4,15 (4H; m); 4,22 (1H; brs); 7,02 (2H; d; J = 8,1 Hz); 7,15 (4H; d; J = 8,3 Hz); 7,95 (2H; d; J = 8,5 Hz).

2) El dihidrocloruro de 2-[4-(Metoxicarbonil)fenil]etil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (291 mg, rendimiento 82%) fue obtenido como un sólido blanco de 2-[4-(metoxicarbonil)fenil]etil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,37 g; 0,644 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,8 Hz); 2,14-2,27 (1H; m); 2,35 (3H; s); 2,42 (3H; brs); 2,73 (2H; d; J = 6,4 Hz); 2,91 (2H; brs); 3,81 (2H; d; J = 5,3 Hz); 3,85 (3H; s); 4,17 (2H; t; J = 6,5 Hz); 7,12 (2H; d; J = 6,8 Hz); 7,22 (2H; d; J = 7,9 Hz); 7,29 (2H; d; J = 8,3 Hz); 7,89 (2H; d; J = 8,3 Hz); 8,34 (3H; brs).

Ejemplo 270

Dihidrocloruro de ácido 4-[2-({[5-(aminometil)-6-isobutil-2-

metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)etil]benzoico

1) El ácido 4-[2-({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)etil]benzoico (1,30 g; rendimiento 95%) fue obtenido como un aceite incoloro de 2-[4-(metoxicarbonil)fenil]etil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,40 g; 2,44 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,16-2,27 (1H; m); 2,37 (3H; s); 2,44 (3H; s); 2,70 (2H; d; J = 6,9 Hz); 2,79 (2H; d; J = 7,2 Hz); 4,11-4,18 (4H; m); 4,24 (1H; brs); 7,02 (2H; d; J = 7,9 Hz); 7,15-7,20 (4H; m); 8,01 (2H; d; J = 8,3 Hz).

2) El dihidrocloruro de ácido 4-[2-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)etil]benzoico (359 mg, rendimiento 94%) fue obtenido como un sólido blanco de ácido 4-[2-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)etil]benzoico (0,40 g; 0,713 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,14-2,25 (1H; m); 2,35 (3H; s); 2,42 (3H; s); 2,71 (2H; t; J = 6,5 Hz);

2,87 (2H; d; J = 7,0 Hz); 3,80 (2H; d; J = 5,3 Hz); 4,16 (2H; t; J = 6,5 Hz); 7,11 (2H; d; J = 8,1 Hz); 7,21-7,26 (4H; m); 7,87 (2H; d; J = 8,1 Hz); 8,28 (3H; brs).

Ejemplo 271

Dihidrocloruro de 2-[4-(aminocarbonil)fenil]etil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) El 2-[4-(Aminocarbonil)fenil]etil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (598 mg, rendimiento 99%) fue obtenido como un aceite incoloro de ácido 4-[2-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)etil]benzoico (0,60 g; 1,07 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,16-2,27 (1H; m); 2,37 (3H; s); 2,47 (3H; s); 2,66 (2H; t; J = 7,1 Hz); 2,78 (2H; d; J = 7,2 Hz); 4,09-4,15 (4H; m); 4,24 (1H; brs); 5,67 (1H; brs); 6,06 (1H; brs); 7,02 (2H; d; J = 7,9 Hz); 7,15-7,19 (4H; m); 7,73 (2H; d; J = 8,1 Hz).

2) El dihidrocloruro de 2-[4-(Aminocarbonil)fenil]etil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (508 mg, rendimiento 90%) fue obtenido como un sólido blanco de 2-[4-(aminocarbonil)fenil]etil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (598 mg; 1,06 mmol) según un método

similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,16-2,25 (1H; m); 2,36 (3H; s); 2,42 (3H; brs); 2,67 (2H; t; J = 6,4 Hz); 2,87 (2H; brs); 3,81 (2H; d; J = 5,5 Hz); 4,16 (2H; t; J = 6,5 Hz); 7,11 (2H; d; J = 7,7 Hz); 7,18-7,25 (4H; m); 7,32 (1H, brs); 7,81 (2H, d; J = 8,3 Hz); 7,95 (1H; brs); 8,27 (3H; brs).

Ejemplo 272

3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzamida

1) El Terc-butil {[5-{[3-(aminocarbonil)fenoxi]metil}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (240 mg, rendimiento 80%) fue obtenido como un sólido blanco de ácido 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}benzoico (0,30 g; 0,578 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,21-2,28 (1H; m); 2,35 (3H; s); 2,62 (3H; s); 2,79 (2H; d; J = 7,2 Hz); 4,09-4,11 (2H; m); 4,22 (1H; brs); 4,68 (2H; s); 5,55 (1H; brs); 6,01 (1H; brs); 6,96-7,01 (1H; m); 7,04 (2H; d, J = 7,9 Hz), 7,17 (2H; d; J = 7,7 Hz); 7,29-7,32 (2H; m); 8,02 (1H, s).

2) 3-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-

metilfenil)piridin-3-il]metoxi}benzamida (166 mg, rendimiento 85%) fue obtenido como un sólido blanco del terc-butil {[5-{[3-(aminocarbonil)fenoxi]metil}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (240 mg; 0,463 mmol) según un método similar al método del Ejemplo 239-2).

^{1}H-RMN ($CDCl_3$) δ:1,00 (6H; d; J = 6,8 Hz); 2,21-2,30 (1H; m); 2,36 (3H; s); 2,61 (3H; s); 2,81 (2H; d; J = 7,2 Hz); 3,60 (2H; s); 4,68 (2H; s); 5,52 (1H; brs); 6,06 (1H; brs); 6,96-7,00 (1H; m); 7,09 (2H; d; J = 7,9 Hz); 7,18 (2H; d; J = 7,9 Hz), 7,25-7,31 (3H; m).

Ejemplo 273

Metil 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metilbenzoato dihidrocloruro de

1) Metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metilbenzoato (720 mg, rendimiento 52%) fue obtenido como polvo blanco del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,0 g; 2,51 mmol) y metil 2-hidroxi-5-metilbenzoato (500 mg; 3,01 mmol) según un método similar al método del Ejemplo 214-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,17-2,26 (1H; m); 2,27 (3H; s); 2,37 (3H; s); 2,67 (3H; s); 2,78 (2H; d; J = 7,2 Hz); 3,80 (3H; s); 4,09 (2H; d; J = 4,9 Hz);

4,20 (1H; brs); 4,68 (2H; s); 7,02-7,06 (3H; m); 7,11 (1H; dd; J = 8,5; 1,9 Hz); 7,16 (2H; d; J = 7,7 Hz); 7,52 (1H; d; J = 1,9 Hz).

2) Dihidrocloruro de metil 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metilbenzoato (100 mg, rendimiento 70%) fue obtenido como polvo blanco de metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metilbenzoato (150 mg; 0,274 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:1,03 (6H; d; J = 6,2 Hz); 2,18-2,24 (1H; m); 2,24 (3H; s); 2,37 (3H; s); 2,99 (3H; s); 3,29 (2H; d; J = 7,2 Hz); 3,70-3,76 (5H; m); 4,78 (2H; s); 6,78 (1H; d; J = 8,5 Hz); 7,17-7,40 (5H; m); 7,46 (1H; s); 8,63 (3H; brs).

Ejemplo 274

Dihidrocloruro de metil 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-clorobenzoato

1) Metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-clorobenzoato (0,80 g; rendimiento 71%) fue obtenido como polvo blanco del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,80 g; 2,0 mmol) y 5-clorosalicilato de metilo (0,56 g; 3,0 mmol) según un método similar al método del Ejemplo 106-1).

^{1}H-RMN ($CDCl_3$)δ: 0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,15-

2,30 (1H; m); 2,37 (3H; s); 2,66 (3H; s); 2,78 (2H; d; J = 7,2 Hz); 3,81 (3H; s); 4,09 (2H; d; J = 4,9 Hz); 4,15-4,25 (1H; m); 4,69 (2H; s); 6,57 (1H; d; J = 8,9 Hz); 7,03 (2H; d; J = 8,0 Hz); 7,17 (2H; d; J = 8,0 Hz); 7,26 (1H; dd; J = 2,7; 8,9 Hz); 7,69 (1H; d; J = 2,7 Hz).

2) Una mezcla de metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-clorobenzoato (0,19 g; 0,33 mmol) y solución ácido clorhídrico metanol (4 mL) fue agitada a temperatura ambiente por 3 hrs. La mezcla de reacción fue concentrada bajo presión reducida y el sólido obtenido fue lavado con diisopropil éter para dar dihidrocloruro de metil 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-clorobenzoato (0,17 g; rendimiento 96%) como un polvo blanco.

^{1}H-RMN (DMSO-d_6)δ: 0,99 (6H; d; J = 6,6 Hz); 2,15-2,30 (1H; m); 2,35 (3H; s); 3,08 (3H; brs); 3,08 (2H; brs); 3,75 (3H; s); 3,82 (2H; d; J = 4,5 Hz); 4,79 (2H; s); 6,97 (1H; d; J = 9,0 Hz); 7,24 (2H; d; J = 7,9 Hz); 7,29 (2H; d; J = 7,9 Hz); 7,52 (1H; dd; J = 2,8; 9,0 Hz); 7,65 (1H; d, J = 2,8 Hz), 8,35 (3H; brs).

Ejemplo 275

Dihidrocloruro de metil 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metoxibenzoato

1) Metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-

isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metoxibenzoato (0,70 g; rendimiento 62%) fue obtenido como polvo blanco del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,80 g; 2,0 mmol) y 5-metoxisalicilato de metilo (0,55 g; 3,0 mmol) según un método similar al método del Ejemplo 106-1).

^{1}H-RMN ($CDCl_3$)δ: 0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,15-2,30 (1H; m); 2,38 (3H; s); 2,69 (3H; s); 2,78 (2H; d; J = 7,2 Hz); 3,77 (3H; s); 3,81 (3H; s); 4,09 (2H; d; J = 4,7 Hz); 4,15-4,30 (1H; m); 4,68 (2H; s); 6,50 (1H; d; J = 9,0 Hz); 6,85 (1H; dd; J = 3,2; 9,0 Hz); 7,01 (2H; d; J = 7,9 Hz); 7,17 (2H; d; J = 7,9 Hz); 7,24 (1H; d; J = 3,2 Hz).

2) Dihidrocloruro de metil 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metoxibenzoato (0,20 g; rendimiento 96%) fue obtenido como polvo blanco de metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metoxibenzoato (0,23 g; 0,40 mmol) según un método similar al método del Ejemplo 274-2).

^{1}H-RMN (DMSO-d_6)δ: 0,98 (6H; d; J = 6,6 Hz); 2,15-2,30 (1H; m); 2,37 (3H; s); 2,73 (3H; brs); 2,93 (2H; brs); 3,72 (3H; s); 3,73 (3H; s); 3,79 (2H; d; J = 4,9 Hz); 4,69 (2H; brs); 6,77 (1H; d; J = 9,0 Hz); 7,01 (1H; dd; J = 3,2; 9,0 Hz); 7,14 (1H; d; J = 3,2 Hz); 7,20 (2H; d; J = 7,8 Hz); 7,29 (2H;

d; J = 7,8 Hz); 8,11 (3H; brs).

Ejemplo 276

Dihidrocloruro de ácido 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-4-metoxibenzoico

1) Metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-4-metoxibenzoato (0,81 g; rendimiento 72%) fue obtenido como polvo blanco del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,80 g; 2,0 mmol) y 4-metoxisalicilato de metilo (0,55 g; 3,0 mmol) según un método similar al método del Ejemplo 106-1),

1H-NMR (CDCl3)d: 0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,15-2,30 (1H; m); 2,36 (3H; s); 2,68 (3H; s); 2,78 (2H; d; J = 7,2 Hz); 3,75 (3H; s); 3,77 (3H; s); 4,09 (2H; d; J = 4,7 Hz); 4,20-4,25 (1H; m); 4,68 (2H; s); 6,14 (1H; d; J = 2,4 Hz); 6,48 (1H; dd; J = 2,4; 8,7 Hz); 7,00-7,10 (2H; m); 7,15-7,20 (2H; m); 7,79 (1H; d; J = 8,7 Hz).

2) El ácido 2-{[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-4-metoxibenzoico (0,19 g; rendimiento 37%) fue obtenido como polvo blanco de metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-4-metoxibenzoato (0,51 g; 0,91 mmol) según un método similar al método del Ejemplo 36-1).

^{1}H-RMN ($CDCl_3$)δ: 0,99 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,15-2,35 (1H; m); 2,35 (3H; s); 2,64 (3H; s); 2,81 (2H; d; J = 7,2 Hz); 3,82 (3H; s); 4,09 (2H; d; J = 4,9 Hz); 4,15-4,30 (1H; m); 4,87 (2H; s); 6,30 (1H; d; J = 2,3 Hz); 6,63 (1H; dd; J = 2,3; 8,9 Hz); 7,00 (2H; d; J = 7,9 Hz); 7,18 (2H; d; J = 7,9 Hz); 8,12 (1H; d; J = 8,9 Hz); 10,42 (1H; brs).

3) Una mezcla de ácido 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-4-metoxibenzoico (0,15 g; 0,28 mmol) y 6N ácido clorhídrico (4 mL) fue agitado a temperatura ambiente por 6 hrs. La mezcla de reacción fue concentrada bajo presión reducida y el sólido obtenido fue lavado con acetonitrilo para dar dihidrocloruro de ácido 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-4-metoxibenzoico (0,12 g; rendimiento 81%) como un polvo blanco.

^{1}H-RMN (DMSO-d_6)δ: 0,99 (6H; d; J = 6,6 Hz); 2,10-2,30 (1H; m); 2,37 (3H; s); 2,86 (3H; brs); 3,06 (2H; brs); 3,73 (3H; s); 3,82 (2H; brs); 4,76 (2H; brs); 6,31 (1H; d; J = 2,1 Hz); 6,60 (1H; dd; J = 2,1; 8,7 Hz); 7,26 (2H; d; J = 7,2 Hz); 7,32 (2H; d; J = 7,2 Hz); 7,68 (1H; d; J = 8,7 Hz); 8,28 (3H; brs).

Ejemplo 277

Trihidrocloruro de metil 6-({[5-(aminometil)-6-isobutil-2-

metil-4-(4-metilfenil)piridin-3-il]metoxi}metil)nicotinato

1) Una mezcla de terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,50 g; 3,76 mmol), trietilamina (1,05 mL; 7,52 mmol) y tetrahidrofurano (50 mL) fue enfriada a 0°C y fue agregado cloruro de metansulfonilo (647 mg; 5,65 mmol) por gotas. Después de agitar a temperatura ambiente por 30 min., la mezcla de reacción fue vertida en carbonato de hidrógeno de sodio acuoso saturado, y la mezcla se extrajo con acetato de etilo. El extracto fue secado sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida para dar metansulfonato [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilo como un producto en bruto. El producto en bruto fue agregado a una solución de (5-bromopiridin-2-il)metanol (848 mg; 4,51 mmol) e hidruro de sodio (60% en aceite; 226 mg; 5,65 mmol) en tetrahidrofurano (50 mL) y la mezcla fue agitada a 60°C por 1 hr. La mezcla de reacción fue diluida con acetato de etilo, fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar terc-butil {[5-{[(5-bromopiridin-2-il)metoxi]metil}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,35 g;

rendimiento 63%) como un sólido blanco.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,15-2,24 (1H; m); 2,41 (3H; s); 2,65 (3H; s); 2,75 (2H; d; J = 7,4 Hz); 4,06 (2H; d; J = 4,9 Hz); 4,23 (2H; s); 4,39 (2H; s); 7,01 (2H; d; J = 7,9 Hz); 7,16-7,20 (3H; m); 7,73 (1H; dd; J = 8,4; 2,4 Hz); 8,54 (1H; d; J = 2,1 Hz).

2) El metil 6-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}metil)nicotinato (1,15 g; rendimiento 88%) fue obtenido como un aceite amarillo del terc-butil {[5-({[(5-bromopiridin-2-il)metoxi]metil}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,35 g; 2,37 mmol) según un método similar al método del Ejemplo 231-2).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,16-2,25 (1H; m); 2,40 (3H; s); 2,67 (3H; s); 2,76 (2H; d; J = 7,2 Hz); 3,95 (3H; s); 4,06 (2H; d; J = 4,9 Hz); 4,20 (1H; brs); 4,27 (2H; s); 4,50 (2H; s); 7,02 (2H; d; J = 7,9 Hz); 7,19 (2H; d; J = 7,7 Hz); 7,36 (1H; d; J = 8,1 Hz); 8,21 (1H; dd; J = 8,1; 2,1 Hz); 9,08 (1H; d; J = 1,7 Hz).

3) El trihidrocloruro de metil 6-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}metil)nicotinato (114 mg, rendimiento 58%) fue obtenido como un sólido blanco de metil 6-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-

metilfenil)piridin-3-il]metoxi}metil)nicotinato (0,19 g; 0,347 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,11-2,22 (1H; m); 2,38 (3H; s); 3,14 (2H; brs); 3,81 (2H; d; J = 5,3 Hz); 3,90 (3H; s); 4,29 (2H; s); 4,51 (2H; s); 7,23 (2H; d; J = 7,9 Hz); 7,32 (2H; d; J = 7,9 Hz); 7,38 (1H; d; J = 8,1 Hz); 8,25 (1H; dd; J = 8,1; 2,2 Hz); 8,38 (3H; brs); 8,98 (1H; d; J = 1,5 Hz)-

Ejemplo 278

Trihidrocloruro de ácido 6-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}metil)nicotínico

1) El ácido 6-({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}metil)nicotínico (760 mg, rendimiento 81%) fue obtenido como un aceite incoloro de metil 6-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}metil)nicotinato (0,96 g; 1,75 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,14-2,26 (1H; m); 2,39 (3H; s); 2,71 (3H; s); 2,85 (2H; d; J = 7,2 Hz); 4,05-4,10 (2H; m); 4,29 (3H; brs); 4,52 (2H; s); 7,03 (2H; d; J = 7,9 Hz); 7,38 (1H; d; J = 8,1 Hz); 8,29 (1H; dd; J = 8,2; 1,8 Hz); 9,15 (1H; d; J = 1,5 Hz).

2) El trihidrocloruro de ácido 6-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}metil)nicotínico (259 mg, rendimiento 90%) fue obtenido como un sólido blanco de trihidrocloruro de ácido 6-({[5-({[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}metil)nicotínico (0,28 g; 0,525 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,4 Hz); 2,11-2,22 (1H; m); 2,39 (3H; s); 2,94 (3H; brs); 3,13-3,22 (2H; m); 3,81 (2H; brs); 4,29 (2H; brs); 4,51 (2H; s); 7,19-7,25 (2H; m); 7,30-7,36 (3H; m); 8,19-8,24 (1H; m); 8,43 (3H; brs); 8,93-8,96 (1H; m).

Ejemplo 279

Dihidrocloruro de metil 2-{2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]etil}benzoato

1) A una solución de terc-butil ([5-formil-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil)carbamato (0,36 g; 0,908 mmol) y dietil (2-bromobencil)fosfonato (363 mg; 1,18 mmol) en N,N-dimetilformamida (10 mL) fue agregado el metóxido de sodio (165 mg; 4,08 mmol) y la mezcla fue agitada a la temperatura ambiente por 1 hr. La mezcla de reacción fue diluída con acetato de etilo, fue lavada con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y

el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar terc-butil {[5-[(E)-2-(2-Bromofenil)vinil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (390 mg, rendimiento 78%) como un sólido blanco.

^{1}H-RMN ($CDCl_3$) δ:1,00 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,18-2,30 (1H; m); 2,39 (3H; s); 2,72 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 4,11 (2H; d; J = 5,1 Hz); 4,24 (1H; brs); 6,55 (1H; d; J = 16,6 Hz); 6,78 (1H; d; J = 16,6 Hz); 7,02 (2H; d; J = 7,9 Hz); 7,05-7,08 (1H; m); 7,15-7,18 (2H; m); 7,22 (2H; d; J = 7,7 Hz); 7,50 (1H; d; J = 7,5 Hz).

2) El metil 2-{(E)-2-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]vinil}benzoato (280 mg, rendimiento 74%) fue obtenido como un aceite amarillo del terc-butil {[5-[(E)-2-(2-Bromofenil)vinil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (390 mg; 0,907 mmol) según un método similar al método del Ejemplo 231-2).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,18-2,27 (1H; m); 2,39 (3H; s); 2,74 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 3,89 (3H; s); 4,11 (2H; d; J = 5,3 Hz); 4,24 (1H; brs); 6,47 (1H; d; J = 16,8 Hz); 7,02 (2H; d; J = 7,9 Hz); 7,13 (1H; d; J = 7,5 Hz); 7,20-7,29 (4H; m); 7,35-7,40 (1H; m); 7,86 (1H; dd; J = 7,8; 1,4 Hz).

3) Una mezcla de metil 2-{(E)-2-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]vinil}benzoato (0,28 g; 0,53 mmol), 10% paladio-carbono (57 mg; 0,053 mmol) y metanol (10 mL) fue agitada en un tubo sellado bajo una atmósfera de hidrógeno a 5,098 kg/cm^2 a la temperatura ambiente por 3 hrs. La mezcla de reacción fue filtrada y el filtrado fue concentrado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar metil 2-{2-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]etil}benzoato (250 mg, rendimiento 88%) como un sólido blanco.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,14-2,23 (1H; m); 2,43 (3H; s); 2,60 (3H; s); 2,62-2,68 (2H; m); 2,73 (2H; d; J = 7,4 Hz); 2,91-2,96 (2H; m); 3,82 (3H; s); 4,01 (2H; d; J = 5,1 Hz); 4,21 (1H; brs); 6,54 (1H; dd; J = 7,4; 1,2 Hz); 6,94 (2H; d; J = 8,1 Hz); 7,15-7,25 (4H; m); 7,77 (1H; dd; J = 7,6; 1,6 Hz).

4) El dihidrocloruro de metil 2-{2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]etil}benzoato (201 mg, rendimiento 84%) fue obtenido como un sólido blanco de metil 2-{2-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]etil}benzoato (0,25 g; 0,471 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,11-2,20 (1H; m); 2,45 (3H; s); 2,63-2,72 (2H; m); 2,83-2,90 (5H; m); 2,91-2,96 (2H; m); 3,18 (2H; brs); 3,73-3,84 (5H; m); 6,65 (1H; d; J = 7,4 Hz); 7,26 (2H; d; J = 7,7 Hz); 7,31 (1H; dd; J = 7,4; 1,4 Hz); 7,35 (1H; dd; J = 7,4; 1,8 Hz); 7,42 (2H; d; J = 7,9 Hz); 7,75 (1H; dd; J = 7,5; 1,5 Hz); 8,46 (3H; brs).

Ejemplo 280

Dihidrocloruro de metil 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}oxi)metil]benzoato

1) El metil 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}oxi)metil]benzoato (258 mg, rendimiento 64%) fue obtenido como polvo blanco de ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acético (300 mg; 0,703 mmol) y metil 4-(bromometil)benzoato (209 mg; 0,914 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,17-2,26 (1H; m); 2,38 (3H; s); 2,49 (3H; s); 2,77 (2H; d; J = 7,0 Hz); 3,42 (3H; s); 3,93 (3H; s); 4,03 (2H; d; J = 5,1 Hz); 5,09 (2H; s); 6,92 (2H; d; J = 8,1 Hz); 7,16 (2H; d; J = 8,1 Hz); 7,28 (2H; d; J = 8,1 Hz); 8,01 (2H; d; J = 8,1 Hz).

2) El dihidrocloruro de metil 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-

il]acetil}oxi)metil]benzoato (60 mg, rendimiento 92%) fue obtenido como polvo blanco de metil 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}oxi)metil]benzoato (68,6 mg; 0,119 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,98 (6H; d; J = 6,6 Hz); 2,17-2,23 (1H; m); 2,38 (3H; s); 2,85 (3H; s); 3,25 (2H; d; J = 6,8 Hz); 3,63 (2H; s); 3,79 (2H; d; J = 4,5 Hz); 3,87 (3H; s); 5,13 (2H; s); 7,13 (2H; d; J = 7,9 Hz); 7,30 (2H; d; J = 7,9 Hz); 7,39 (2H; d; J = 8,3 Hz); 7,97 (2H; d; J = 8,3 Hz); 8,63 (3H; brs).

Ejemplo 281

Dihidrocloruro de ácido 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metilbenzoico

1) El ácido 2-{[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metilbenzoico (450 mg, rendimiento 86%) fue obtenido como polvo blanco de metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metilbenzoato (537 mg; 0,982 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,18-

2,30 (1H; m); 2,32 (3H; s); 2,34 (3H; s); 2,64 (3H; s); 2,80 (2H; d; J = 7,4 Hz); 4,10 (2H; d; J = 4,9 Hz); 4,20 (1H; s); 4,88 (2H; s); 6,72 (1H; d; J = 8,5 Hz); 7,01 (2H; d; J = 8,1 Hz); 7,18 (2H; d; J = 8,1 Hz); 7,23-7,25 (1H; m); 7,97 (1H; d, J = 2,26 Hz).

2) Dihidrocloruro de ácido 2-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metilbenzoico (150 mg, rendimiento 94%) fue obtenido como polvo blanco del ácido 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metilbenzoico (168 mg; 0,316 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:1,02 (6H; d; J = 6,6 Hz); 2,18-2,30 (1H; m); 2,24 (3H; s); 2,38 (3H; s); 3,00 (3H; s); 3,30 (2H; d; J = 6,8 Hz); 3,87 (2H; d; J = 2,6 Hz); 4,78 (2H; s); 6,72 (1H; d; J = 8,5 Hz); 7,20-7,22 (1H; m); 7,30-7,34 (4H; m); 7,43 (1H; d; J = 1,5 Hz); 8,63 (3H; brs).

Ejemplo 282

Dihidrocloruro de metil 3-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}oxi)metil]benzoato

1) El metil 3-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}oxi)metil]benzoato (401 mg, rendimiento 64%) fue obtenido como polvo blanco de ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-

metilfenil)piridin-3-il]acético (466 mg; 1,09 mmol) y metil 3-(bromometil)benzoato (325 mg; 1,42 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0.96 (6H; d; J = 6.6 Hz); 1.38 (9H; s); 2.17-2.26 (1H; m); 2,36 (3H; s); 2,48 (3H; s); 2,74 (2H; d; J = 7,4 Hz); 3,41 (2H; s); 3,93 (3H; s); 4,03 (2H; d; J = 4,9 Hz); 4,20 (1H; brs); 5,08 (2H; s); 6,90-6,93 (2H; m); 7,14 (2H; d; J = 7,7 Hz); 7,40-7,44 (2H; m); 7,93 (1H; d; J = 0,8 Hz); 7,98-8,01 (1H; m).

2) El dihidrocloruro de metil 3-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}oxi)metil]benzoato (80 mg, rendimiento 99%) fue obtenido como polvo blanco de metil 3-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}oxi)metil]benzoato (84,6 mg; 0,147 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,98 (6H; d; J = 6,6 Hz); 2,17-2,26 (1H; m); 2,36 (3H; s); 2,88 (3H; s); 3,30 (2H; d; J = 6,8 Hz); 3,60 (2H; s); 3,80 (2H; d; J = 3,8 Hz); 3,88 (3H; s); 5,13 (2H; s); 7,12 (2H; d; J = 7,9 Hz); 7,27 (2H; d; J = 7,9 Hz); 7,56-7,60 (2H; m); 7,89 (1H; s); 7,95-7,98 (1H; m); 8,63 (3H, brs).

Ejemplo 283

Dihidrocloruro de 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-4-metoxibenzamida

1) Terc-butil {[5-{[2-(aminocarbonil)-5-metoxifenoxi]metil}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,31 g; rendimiento 82%) fue obtenido como polvo blanco de ácido 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-4-metoxibenzoico (0,38 g; 0,68 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$)δ: 0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,15-2,30 (1H; m); 2,36 (3H; s); 2,63 (3H; s); 2,80 (2H; d; J = 7,2 Hz); 3,80 (3H; s); 4,10 (2H; d; J = 5,1 Hz); 4,20-4,25 (1H; m); 4,75 (2H; s); 5,51 81H; brs); 6,26 (1H; d; J = 2,3 Hz); 6,58 (1H; dd; J = 2,3; 8,9 Hz); 7,00 (2H; d; J = 7,9 Hz); 7,18 (2H; d; J = 7,9 Hz); 7,41 (1H; brs); 8,18 (1H; d; J = 8,9 Hz).

2) El dihidrocloruro de 2-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-4-metoxibenzamide (0.22 g; rendimiento 91%) fue obtenido como polvo blanco del terc-butil {[5-{[2-(aminocarbonil)-5-metoxifenoxi]metil}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,25 g; 0,46 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ: 0,99 (6H; d; J = 6,6 Hz); 2,10-2,30 (1H;

m); 2,35 (3H; s); 2,78 (3H; brs); 3,01 (2H; brs); 3,74 (3H; s); 3,80 (2H; d; J = 5,1 Hz); 4,82 (2H; s); 6,42 (1H; d; J = 2,2 Hz); 6,63 (1H; dd; J = 2,2; 8,7 Hz); 7,14 (2H; brs); 7,15-7,35 (4H; m); 7,74 (1H; d; J = 8,7 Hz); 8,28 (3H; brs).

Ejemplo 284

dihidrocloruro de metil 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-naftoato

1) El metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-naftoato (1,07 g; rendimiento 73%) fue obtenido como polvo blanco del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,0 g; 2,51 mmol) y metil 3-hidroxi-2-naftoato (609 mg, 3,01 mmol) según un método similar al método del Ejemplo 214-1).

^{1}H-RMN ($CDCl_3$) δ:1,00 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,18-2,31 (1H; m); 2,34 (3H; s); 2,70 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 3,87 (3H; s); 4,11 (2H; d; J = 4,7 Hz); 4,20 (1H; brs); 4,81 (2H; s); 6,91 (1H; s); 7,09 (2H; d; J = 7,9 Hz); 7,16 (2H; d; J = 7,9 Hz); 7,34-7,38 (1H; m); 7,46-7,50 (1H; m); 7,58-7,62 (1H; m); 7,79 (1H; d; J = 8,1 Hz); 8,22 (1H; s).

2) El dihidrocloruro de metil 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-naftoato (178 mg, rendimiento 84%) fue obtenido como polvo blanco de metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-

isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-naftoato (220 mg; 0,378 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:1,05 (6H; d; J = 6,2 Hz); 2,18-2,33 (1H; m); 2,34 (3H; s); 3,06 (3H; s); 3,36 (2H; d; J = 6,0 Hz); 3,84 (3H; s); 3,91 (2H;s); 4,96 (2H; s); 7,35-7,45 (6H; m); 7,58 (1H; t; J = 7,35 Hz); 7,79 (1H; d; J = 8,1 Hz); 7,98 (1H; d; J = 7,9 Hz); 8,32 (1H; s); 8,63 (3H; brs).

Ejemplo 285

Dihidrocloruro de ácido 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-naftoico

1) El ácido 3-{[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-naftoico (860 mg, rendimiento 100%) fue obtenido como polvo blanco de metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-naftoato (817 mg; 1,40 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:1,02 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,20-2,30 (1H; m); 2,32 (3H; s); 2,81 (3H; s); 2,97 (2H; d; J = 6,4 Hz); 4,15 (2H; d; J = 3;0 Hz); 4;20 (1H; brs); 5;01 (2H; s); 7;06 (3H; d; J = 7;7 Hz); 7;18 (2H; d; J = 7;7 Hz); 7;40-7,48 (1H; m); 7,52-7,58 (1H; m); 7,62-7,68 (1H; m); 7,89 (1H; d; J = 8,1 Hz); 8,67 (1H; s).

2) El dihidrocloruro de ácido 3-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-naftoico (300 mg, rendimiento 98%) fue obtenido como polvo blanco de ácido 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-naftoico (320 mg; 0,563 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:1,00 (6H; d; J = 6,4 Hz); 2,17-2,29 (1H; m); 2,33 (3H; s); 2,81 (3H; s); 2,90 (2H; s); 3,83 (2H; s); 4,86 (2H; s); 7,24 (1H; s); 7,26-7,33 (4H; m); 7,41 (1H; t; J = 7,5 Hz); 7,53 (1H; t; J = 7,5 Hz); 7,75 (1H; d; J = 8,1 Hz); 7,94 (1H; d; J =8,1 Hz); 8,52 (1H; s); 8,63 (3H; brs).

Ejemplo 286

Dihidrocloruro de 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metilbenzamida

1) Terc-butil {[5-{[2-(aminocarbonil)-4-metilfenoxi]metil}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (250 mg, rendimiento 91%) fue obtenido como polvo blanco del ácido 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metilbenzoico (276 mg; 0,518 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,17-2,28 (1H; m); 2,31 (3H; s); 2,35 (3H; s); 2,64 (3H; s); 2,81

(2H; s); 4,11 (2H; s); 4,20 (1H; s); 4,76 (2H; s); 6,66 (1H; d; J = 8,5 Hz); 7,00 (2H; d; J = 8,1 Hz); 7,17 (2H; d; J = 8,1 Hz); 7,55 (2H; s); 8,00 (2H; s).

2) El dihidrocloruro de 2-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-metilbenzamida (200 mg, rendimiento 92%) fue obtenido como polvo blanco del terc-butil {[5-{[2-(aminocarbonil)-4-metilfenoxi]metil}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (230 mg; 0,433 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:1,01 (6H; d; J = 6,4 Hz); 2,10-2,30 (4H; m); 2,36 (3H; s); 2,96 (3H; s); 3,27 (2H; d; J = 7,0 Hz); 3,86 (2H; d; J = 4,5 Hz); 4,72-4,84 (2H; m); 6,76 (1H; d; J = 8,5 Hz); 7,15 (1H; dd; J = 8,5; 1,9 Hz); 7,25-7,38 (4H; m); 7,42 (1H; d; J = 1,9 Hz); 8,64 (3H; brs).

Ejemplo 287

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetamida

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetamida (198 mg, rendimiento 95%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de acetilo (53 mL; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 1,76 (3H; s); 2,13-2,22 (1H; m); 2,39 (3H; s); 2,55 (3H; s); 3,02 (2H; brs); 3,82 (2H; s); 7,17 (2H; d; J = 7,5 Hz); 7,33 (2H; d; J = 7,5 Hz); 8,31 (3H; brs); 9,50 (1H; brs).

Ejemplo 288

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]propanamida

Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]propanamida (195 mg, rendimiento 93%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de propionilo (65 mL; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:0,82 (3H; t; J = 6,9 Hz); 0,98 (6H; d; J = 6,6 Hz); 2,02 (2H; q; J = 6,9 Hz); 2,08-2,32 (1H; m); 2,38 (3H; s); 2,55 (3H; s); 3,06 (2H; brs); 3,83 (2H; s); 7,17 (2H; d; J = 7,8 Hz); 7,32 (2H; d; J = 7,8 Hz); 8,37 (3H; brs), 9.49 (1H, brs).

Ejemplo 289

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2,2-dimetilpropanamida

Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2,2-dimetilpropanamida (184 mg,

rendimiento 72%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de pivaloilo (92 µL; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:0,89 (9H; s); 0,98 (6H; d; J = 6,6 Hz); 2,12-2,24 (1H; m); 2,36 (3H; s); 2,51 (3H; s); 2,97 (2H; brs); 3,81 (2H; s); 7,14 (2H; d; J = 8,1 Hz); 7,28 (2H; d; J = 8,1 Hz); 8,28 (3H; brs); 8,95 (1H; brs).

Ejemplo 290

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]ciclopropancarboxamida

Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]ciclopropancarboxamida (170 mg, rendimiento 85%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de ciclopropancarbonilo (68 µL; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:0,58-0,67 (4H; m); 0,98 (6H; d; J = 6,6 Hz); 1,51-1,58 (1H; m); 2,17-2,26 (1H; m); 2,39 (3H; s); 2,54 (3H; s); 3,02 (2H; brs); 3,81 (2H; s); 7,16 (2H; d; J = 7,5 Hz); 7,32 (2H; d; J = 7,5 Hz); 8,32 (3H; brs); 9,70 (1H; brs).

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Ejemplo 291

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]ciclopentancarboxamida

Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]ciclopentancarboxamida (137 mg, rendimiento 62%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de ciclopentancarbonilo (68 µL; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 0,98 (6H; d; J = 6,6 Hz); 1,30-1,62 (9H; m); 2,15-2,24 (1H; m); 2,38 (3H; s); 2,50 (3H; s); 3,02 (2H; brs); 3,81 (2H; s); 7,15 (2H; d; J = 7,8 Hz); 7,30 (2H; d; J = 7,8 Hz); 8,32 (3H; brs); 9,39 (1H; brs).

Ejemplo 292

Trihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]piridin-2-carboxamida

Trihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]piridin-2-carboxamida (218 mg, rendimiento 91%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de piridin-2-carbonilo (106 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 1,01 (6H; d; J = 6,6 Hz); 2,20-2,28 (1H; m); 2,28 (3H; s); 2,64 (3H; s); 3,14 (2H; brs); 3,86 (2H; s); 7,20-7,27 (4H; m); 7,06-7,65 (1H; m); 7,94-8,02 (2H; m); 8,43 (3H; brs); 8,61 (1H; d; J = 4,8 Hz); 10,33 (1H; s).

Ejemplo 293

Trihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]nicotinamida

Trihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]nicotinamida (225 mg, rendimiento 94%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de nicotinoilo (106 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 1,02 (6H; d; J = 6,6 Hz); 2,23-2,31 (1H; m); 2,31 (3H; s); 2,73 (3H; s); 3,19 (2H; brs); 3,90 (2H; s); 7,28 (4H; s); 7,73-7,78 (1H; m); 8,35 (2H; d; J = 8,1 Hz); 8,53 (3H; brs); 8,85 (1H; d; J = 3,6 Hz); 8,94 (1H; s); 10,90 (1H, brs).

Ejemplo 294

Trihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]isonicotinamida

Trihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]isonicotinamida (215 mg,

rendimiento 91%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de isonicotinoilo (106 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 1,01 (6H; d; J = 6,6 Hz); 2,22-2,31 (1H; m); 2,31 (3H; s); 2,70 (3H; s); 3,51 (2H; brs); 3,88 (2H; s); 7,28 (4H; s); 7,87 (2H; d; J = 6,0 Hz); 8,51 (3H; brs); 8,88 (2H; d; J = 6,0 Hz); 11,20 (1H; brs).

Ejemplo 295

Dihidrocloruro de {[2-isobutil-6-metil-4-(4-metilfenil)-5-(fenoximetil)piridin-3-il]metil}amina

1) Terc-butil {[2-isobutil-6-metil-4-(4-metilfenil)-5-(fenoximetil)piridin-3-il]metil}carbamato (270 mg, rendimiento 56%) fue obtenido como un aceite incoloro de terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,40 g; 1,00 mmol) y fenol (94,5 mg; 1,00 mmol) según un método similar al método del Ejemplo 214-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,18-2,27 (1H; m); 2,36 (3H; s); 2,63 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 4,10 (2H; d; J = 5,7 Hz); 4,22 (1H; brs); 4,62 (2H; s); 6,78-6,82 (2H; m); 6,93 (1H; t; J = 7,4 Hz); 7,05 (2H; d; J = 8,1 Hz); 7,17 (2H; d; J = 7,7 Hz); 7,21-7,24 (2H; m).

2) El dihidrocloruro de {[2-isobutil-6-metil-4-(4-metilfenil)-5-(fenoximetil)piridin-3-il]metil}amina (132 mg, rendimiento 51%) fue obtenido como un aceite incoloro del terc-butil {[2-isobutil-6-metil-4-(4-metilfenil)-5-(fenoximetil)piridin-3-il]metil}carbamato (0,27 g; 0,569 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,17-2,26 (1H; m); 2,35 (3H; s); 2,82 (3H; brs); 3,12 (2H; brs); 3,83 (2H; d; J = 4,9 Hz); 4,70 (2H; s); 6,85 (2H; d; J = 7,9 Hz); 6,95 (1H; t; J = 7,4 Hz); 7,23-7,33 (6H; m); 8,38 (3H; brs).

Ejemplo 296

Trihidrocloruro de 6-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}metil)nicotinamida

1) Terc-butil {[5-({[5-(aminocarbonil)piridin-2-il]metoxi}metil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (370 mg, rendimiento 77%) fue obtenido como un sólido blanco de ácido 6-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}metil)nicotínico (0,48 g; 0,899 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,13-2,23 (1H; m); 2,40 (3H; s); 2,67 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 4,07 (2H; d; J = 5,1 Hz); 4,23 (1H; brs); 4,27 (2H;

s); 4,49 (2H; s); 7,03 (2H; d; J = 7,9 Hz); 7,20 (2H; d; J = 7,7 Hz); 7,38 (1H; d; J = 7,9 Hz); 8,08 (1H; dd; J = 8,1; 2,3 Hz); 8,90 (1H; d; J = 2,3 Hz).

2) El trihidrocloruro de 6-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}metil)nicotinamida (282 mg, rendimiento 75%) fue obtenido como un sólido blanco del terc-butil {[5-({[5-(aminocarbonil)piridin-2-il]metoxi}metil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,37 g; 0,695 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,11-2,24 (1H; m); 2,39 (3H; s); 2,97 (3H; brs); 3,23 (2H; d; J = 5,8 Hz); 3,82 (2H; d; J = 5,3 Hz); 4,30 (2H; s); 4,52 (2H; s); 7,25 (2H; d; J = 8,1 Hz); 7,32 (2H; d; J = 8,1 Hz); 7,39-7,42 (1H; m); 7,61-7,69 (1H; m); 8,27-8,30 (1H; m); 8,50 (3H; brs); 8,99 (1H; brs).

Ejemplo 297

Dihidrocloruro de ácido 4-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}isoftálico

1) Dimetil 4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}isoftalato (1,12 g; rendimiento 75%) fue obtenido como un sólido blanco del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,00 g; 2,51 mmol) y dimetil 4-hidroxiisoftalato (528 mg,

2,51 mmol) según un método similar al método del Ejemplo 214-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,19-2,31 (1H; m); 2,35 (3H; s); 2,66 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 3,83 (3H; s); 3,89 (3H; s); 4,06-4,11 (2H; m); 4,23 (1H; brs); 4,77 (2H; s); 6,71 (1H; d; J = 8,9 Hz); 7,05 (2H; d; J = 8,1 Hz); 7,16 (2H; d; J = 7,9 Hz); 8,01 (1H; dd; J = 8,7; 2,3 Hz); 8,41 (1H; d; J = 2,3 Hz).

2) El ácido 4-{[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}isoftálico (310 mg, rendimiento 90%) fue obtenido como un sólido blanco del dimetil 4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}isoftalato (0,36 g; 0,609 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:1,03 (6H; d; J = 6,4 Hz); 1,37 (9H; s); 2,35 (3H; s); 2,96 (3H; brs); 3,13 (2H; brs); 4,16 (2H; brs); 4,94 (2H; brs); 6,76 (1H; brs); 7,07 (2H; brs); 7,22 (2H; d; J = 7,7 Hz); 8,01 (1H; brs); 8,53 (1H; brs).

3) El dihidrocloruro de ácido 4-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}isoftálico (256 mg, rendimiento 86%) fue obtenido como un sólido blanco de ácido 4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-

metilfenil)piridin-3-il]metoxi}isoftálico (0,31 g; 0,551 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,16-2,28 (1H; m); 2,35 (3H; s); 2,85 (3H; brs); 3,08 (2H; brs); 3,83 (2H; brs); 4,86 (2H; s); 7,01 (1H; d; J = 8,9 Hz); 7,27 (2H; d; J = 8,1 Hz); 7,31 (2H; d; J = 7,7 Hz); 7,97 (1H; dd; J = 8,7; 2,3 Hz); 8,18 (1H; d, J = 2,1 Hz); 8,34 (3H; brs).

Ejemplo 298

Dihidrocloruro de metil 2-{(E)-2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]vinil}benzoato

Dihidrocloruro de metil 2-{(E)-2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]vinil}benzoato (31.4 mg, rendimiento 33%) fue obtenido como un sólido blanco de metil 2-{(E)-2-[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]vinil}benzoato (0,10 g; 0,189 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,01 (6H; d; J = 6,4 Hz); 2,16-2,28 (1H; m); 2,38 (3H; s); 2,86 (3H; brs); 3,06 (2H; brs); 3,83-3,88 (5H; m); 6,53 (1H; d; J = 16,8 Hz); 7,17 (1H; d; J = 16,8 Hz); 7,24 (2H; d; J = 7;7 Hz); 7;29 (1H; d; J = 7;7 Hz); 7;35 (2H; d; J = 7,9 Hz); 7,40 (1H; t; J = 7,5 Hz); 7,53 (1H; t; J = 7,5 Hz); 7,79 (1H; dd; J = 7,8; 1,2 Hz); 8,32 (3H; brs).

Ejemplo 299

Dihidrocloruro de ácido 4-[1-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)etil]benzoico

1) El 1-[4-(Metoxicarbonil)fenil]etil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,02 g; rendimiento 73%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,00 g; 2,42 mmol) y metil 4-(1-hydroxyetil)benzoato (486 mg; 2,42 mmol) según un método similar al método del Ejemplo 247-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,25 (3H; d; J = 7,0 Hz); 1,39 (9H; s); 2,16-2,24 (1H; m); 2,33 (3H; s); 2,48 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 3,92 (3H; s); 4,11-4,16 (2H; m); 4,22 (1H; brs); 5,73-5,79 (1H; m); 6,96-6,99 (1H; m); 7,04-7,09 (2H; m); 7,13-7,17 (3H; m); 7,93 (2H; d; J = 8,3 Hz).

2) El ácido 4-[1-({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)etil]benzoico (950 mg, rendimiento 95%) fue obtenido como un aceite incoloro de 1-[4-(metoxicarbonil)fenil]etil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,02 g; 1,77 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,26 (3H; d; J =

6,8 Hz); 1,39 (9H; s); 2,15-2,26 (1H; m); 2,34 (3H; s); 2,50 (3H; s); 2,79 (2H; d; J = 7,2 Hz); 4,11-4,16 (2H; m); 4,24 (1H; brs); 5,79 (1H; q; J = 6,6 Hz); 7,00-7,13 (4H; m); 7,18 (2H; d; J = 8,1 Hz); 7,99 (2H; d; J = 8,3 Hz).

3) El dihidrocloruro de ácido 4-[1-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)etil]benzoico (259 mg, rendimiento 93%) fue obtenido como un sólido blanco de ácido 4-[1-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)etil]benzoico (0,30 g; 0,522 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,8 Hz); 1,22 (3H; d; J = 6,6 Hz); 2,17-2,26 (1H; m); 2,33 (3H; s); 2,47 (3H; brs); 2,88 (2H; d; J = 5,7 Hz); 3,81 (2H; d; J = 5,5 Hz); 5,76 (1H; q; J = 6,6 Hz); 7,11-7,25 (6H; m); 8,27 (3H; brs).

Ejemplo 300

Dihidrocloruro de [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(metiltio)fenoxi]metil}piridin-3-il)metil]amina

1) Terc-butil [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(metiltio)fenoxi]metil}piridin-3-il)metil]carbamato (1.37 g; rendimiento 70%) fue obtenido como un aceite incoloro del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,50 g; 3,76 mmol) y 2-(metiltio)fenol (573 mg; 3,76 mmol) según un método similar

al método del Ejemplo 214-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,19-2,31 (1H; m); 2,36 (3H; s); 2,37 (3H; s); 2,69 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 4,09-4,11 (2H; m); 4,21 (1H; brs); 4,68 (2H; s); 6,57 (1H; dd; J = 7,9; 1,3 Hz); 6,91-7,04 (2H; m); 7,06-7,12 (3H; m); 7,17 (2H; d; J = 7,7 Hz).

2) El dihidrocloruro de [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(metiltio)fenoxi]metil}piridin-3-il)metil]amina (112 mg, rendimiento 69%) fue obtenido como un sólido blanco del terc-butil [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(metiltio)fenoxi]metil}piridin-3-il)metil]carbamato (0,17 mg; 0,326 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,18-2,27 (1H; m); 2,35 (3H; s); 2,36 (3H; s); 2,88 (3H; brs); 3,15 (2H; brs); 3,83 (2H; brs); 4,75 (2H; s); 6,57 (1H; d; J = 6,8 Hz); 6,96-7,07 (2H; m); 7,13-7,16 (1H; m); 7,28 (2H; d; J = 8,3 Hz); 7,32 (2H; d; J = 7,4 Hz); 8,41 (3H; brs).

Ejemplo 301

Dihidrocloruro de [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(metilsulfonil)fenoxi]metil}piridin-3-il)metil]amina

1) Terc-butil [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(metilsulfonil)fenoxi]metil}piridin-3-il)metil]carbamato (330 mg, rendimiento 81%) fue obtenido como un sólido blanco del

terc-butil [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(metiltio)fenoxi]metil}piridin-3-il)metil]carbamato (0,38 g; 0,730 mmol) según un método similar al método del Ejemplo 91-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,21-2,30 (1H; m); 2,35 (3H; s); 2,67 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 3,08 (3H; s); 4,11 (2H; d; J = 5,1 Hz); 4,27 (1H; brs); 4,79 (2H; s); 6,76 (1H; d; J = 8,1 Hz); 7,06-7,10 (3H; m); 7,18 (2H; d; J = 7,9 Hz); 7,45-7,50 (1H; m); 7,97 (1H; dd; J = 7,7; 1,7 Hz).

2) El dihidrocloruro de [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(metilsulfonil)fenoxi]metil}piridin-3-il)metil]amina (227 mg, rendimiento 59%) fue obtenido como un sólido blanco del terc-butil [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(metilsulfonil)fenoxi]metil}piridin-3-il)metil]carbamato (0,33 g; 0,597 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,4 Hz); 2,17-2,28 (1H; m); 2,35 (3H; s); 2,84 (3H; brs); 3,05-3,17 (5H; m); 3,84 (2H; d; J = 4,7 Hz); 4,87 (2H; s); 7,11 (1H; d; J = 8,3 Hz); 7,18 (1H; t; J = 7,6 Hz); 7,28-7,33 (4H; m); 7,60-7,66 (1H; m); 7,81 (1H; dd; J = 7,7; 1,7 Hz); 8,40 (3H; brs).

Ejemplo 302

Dihidrocloruro de [(2-isobutil-6-metil-4-(4-metilfenil)-5-

{[2-(metilsulfinil)fenoxi]metil}piridin-3-il)metil]amina

1) A una solución mezcla de terc-butil [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(metiltio)fenoxi]metil}piridin-3-il)metil]carbamato (0,47 g; 0,902 mmol) en metanol (10 mL) y agua (10 mL) fue agregado peryodato de sodio (377 mg; 1,76 mmol) y la mezcla fue agitada a la temperatura ambiente durante 2 días. La mezcla de reacción fue diluída con acetato de etilo, fue lavada consecutivamente con agua y solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar terc-butil [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(metilsulfinil)fenoxi]metil}piridin-3-il)metil]carbamato (164 mg, rendimiento 33%) como un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ:1,00 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,21-2,29 (1H; m); 2,35 (3H; s); 2,61 (3H; s); 2,69 (3H; s); 2,80 (2H; d; J = 7,4 Hz); 4,09-4,11 (2H; m); 4,23 (1H; brs); 4,59 (1H; d; J = 10;0 Hz); 4;83 (1H; d; J = 10;0 Hz); 6;71 (1H; d; J = 8,1 Hz); 6,95-6,98 (1H; m); 7,02-7,05 (1H; m); 7,16-7,21 (3H; m); 7,32-7,38 (1H; m); 7,82 (1H; dd; J = 7,7; 1,7 Hz).

2) El dihidrocloruro de [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(metilsulfinil)fenoxi]metil}piridin-3-il)metil]amina (97,4 mg; rendimiento 62%) fue obtenido como un sólido blanco del terc-butil [(2-isobutil-6-metil-4-(4-

metilfenil)-5-{[2-(metilsulfinil)fenoxi]metil}piridin-3-il)metil]carbamato (164 mg; 0,306 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,17-2,27 (1H; m); 2,34 (3H; s); 2,63 (3H; s); 2,77 (3H; brs); 3,06 (2H; brs); 3,82 (2H; brs); 4,70 (1H; d; J = 10,6 Hz); 4,90 (1H; d; J = 10,7 Hz); 6,99 (1H; d; J = 8,1 Hz); 7,20-7,33 (5H; m); 7,42-7,47 (1H; m); 7,64 (1H; dd; J = 7,5; 1,7 Hz); 8,31 (3H; brs).

Ejemplo 303

Dihidrocloruro de 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-naftamida

1) Terc-butil {[5-({[3-(aminocarbonil)-2-naftil]oxi}metil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (230 mg, rendimiento 46%) fue obtenido como polvo blanco de ácido 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-naftoico (500 mg; 0,879 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,89 (6H; d; J = 6,6 Hz); 1,35 (9H; s); 2,07-2,22 (1H; m); 2,28 (3H; s); 2,79 (3H; s); 2,87 (2H; d; J = 7,2 Hz); 4,14-4,21 (3H; m); 4,95 (2H; s); 7,04 (1H; s); 7,08-7,21 (4H; m); 7,42-7,52 (1H; m); 7,63 (1H; d; J = 7,5 Hz); 7,74 (1H; d; J = 7,5 Hz); 7,81 (1H; d; J = 8,1 Hz); 8,67 (1H;

s); 11,73 (2H; s).

2) El dihidrocloruro de 3-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-naftamida (200 mg, rendimiento 91%) fue obtenido como polvo blanco del terc-butil {[5-({[3-(aminocarbonil)-2-naftil]oxi}metil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (230 mg; 0,405 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:1,00 (6H; d; J = 6,4 Hz); 2,17-2,30 (1H; m); 2,32 (3H; s); 2,51 (3H; s); 2,81 (2H; s); 3,83 (2H; s); 4,88 (2H; s); 7,25-7,33 (4H; m); 7,40 (1H; t; J = 7,5 Hz); 7,50 (1H; t; J = 7,5 Hz); 7,75 (1H; d; J = 8,1 Hz); 7,92 (1H; d; J =7,9 Hz); 8,12 (1H; s); 8,42 (1H; s); 8,62 (3H; brs).

Ejemplo 304

5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)-N-fenilnicotinamida

A una solución de ácido 5-({[(benciloxi)carbonil]amino}metil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (523 mg; 1,17 mmol) en tetrahidrofurano (5 mL) fue agregado el cloruro de oxalilo (120 mL; 1,4 mmol) y fue agregada una gota de N,N-dimetilformamida. La solución de la reacción fue agitada por 3 hrs. y la mezcla de reacción fue concentrada. El residuo fue disuelto en tetrahidrofurano (5 mL). Fue agregado anilina (91 mL; 1,0 mmol) y trietilamina (210 µL; 1,5 mmol) y la mezcla fue agitada por

30 min. Fue agregada agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar un aceite. A una solución del aceite en etanol (5 mL) fue agregado 10% paladio - carbono (50 mg) y la mezcla fue agitada bajo atmósfera de hidrógeno a la temperatura ambiente por 3 hrs. La mezcla de reacción fue filtrada y el filtrado fue concentrado. El aceite obtenido fue cristalizado del hexano y dietil éter para dar 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)-N-fenilnicotinamida (320 mg, rendimiento 83%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1,00 (6H; d; J = 6,6 Hz); 2,17-2,31 (1H; m); 2,34 (3H; s); 2,65 (3H; s); 2,82 (2H; d; J = 7,5 Hz); 3,69 (2H; s); 6,93 (1H; brs); 7,04-7,26 (9H; m).

Ejemplo 305

Dihidrocloruro de metil 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxilato

1) El etil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxilato (3,23 g; rendimiento 79%) fue obtenido como un aceite incoloro de terc-butil {[5-

(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (3,00 g; 7,52 mmol) y etil 3-hidroxi-1-metil-1H-pirazol-4-carboxilato (1,28 g; 7,52 mmol) según un método similar al método del Ejemplo 183-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,8 Hz); 1,28 (3H; t; J = 7,1 Hz); 1,39 (9H; s); 2,17-2,26 (1H; m); 2,36 (3H; s); 2,66 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,67 (3H; s); 4,08 (2H; d; J = 4,7 Hz); 4,19-4,26 (3H; m); 4,90 (2H; s); 7,10 (2H; d; J = 8,1 Hz); 7,16 (2H; d; J = 8,1 Hz); 7,61 (1H; s).

2) El ácido 3-{[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxílico (1,58 g; rendimiento 51%) fue obtenido como un sólido blanco etil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxilato (3,23 g; 5,86 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,8 Hz); 1,38 (9H; s); 2,15-2,28 (1H; m); 2,36 (3H; s); 2,66 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 3,71 (3H; s); 4,04-4,09 (2H; m); 4,23 (1H; brs); 4,98 (2H; s); 7,05 (2H; d; J = 8,1 Hz); 7,19 (2H; d; J = 7,7 Hz); 7,69 (1H; s).

3) El ácido 3-{[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-

metil-1H-pirazol-4-carboxílico (0,50 g; 0,957 mmol) fue disuelto en N,N-dimetilformamida (5 mL) y fue agregado yoduro de metilo (176 mg; 1,24 mmol) y carbonato de potasio (0,20 g; 1,44 mmol). La mezcla fue agitada a la temperatura ambiente por 1 hr. Fue agregado acetato de etilo a la mezcla de reacción, y la mezcla fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxilato (470 mg; rendimiento 91%) como un sólido blanco.

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,17-2,26 (1H; m); 2,36 (3H; s); 2,66 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,68 (3H; s); 3,76 (3H; s); 4,08 (2H; d; J = 4,7 Hz); 4,23 (1H; brs); 4,90 (2H; s); 7,10 (2H; d; J = 7,9 Hz); 7,16 (2H; d; J = 7,9 Hz); 7,62 (1H; s).

4) El dihidrocloruro de metil 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxilato (382 mg, rendimiento 85%) fue obtenido como un sólido blanco de metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxilato (0,47 g; 0,876 mmol) según un método similar al

método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,14-2,28 (1H; m); 2,38 (3H; s); 2,90 (3H; brs); 3,16 (2H; brs); 3,65 (3H; s); 3,66 (3H; s); 3,82 (2H; d; J = 5,1 Hz); 4,90 (2H; s); 7,27 (2H; d; J = 8,1 Hz); 7,33 (2H; d; J = 8,1 Hz); 8,09 (1H; s); 8,41 (3H; brs).

Ejemplo 306

Dihidrocloruro de ácido 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxílico

Dihidrocloruro de ácido 3-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxílico (268 mg, rendimiento 94%) fue obtenido como un sólido blanco del ácido 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxílico (0,30 g; 0,574 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,4 Hz); 2,14-2,25 (1H; m); 2,39 (3H; s); 2,88 (3H; brs); 3,14 (2H; brs); 3,64 (3H; s); 3,82 (2H; d; J = 4,7 Hz); 4,87 (2H; s); 7,28 (2H; d; J = 7,9 Hz); 7,34 (2H; d; J = 8,1 Hz); 8,00 (1H; s); 8,38 (3H; brs).

Ejemplo 307

Dihidrocloruro de 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxamida

1) Terc-butil {[5-({[4-(aminocarbonil)-1-metil-1H-pirazol-3-il]oxi}metil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (307 mg, rendimiento 61%) fue obtenido como un aceite incoloro del ácido 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxílico (0,50 g; 0,957 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,19-2,28 (1H; m); 2,37 (3H; s); 2,65 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 3,69 (3H; s); 4,09 (2H; d; J = 4,9 Hz); 4,22 (1H; brs); 4,98 (2H; s); 5,30 (1H; brs); 6,43 (1H; brs); 7,01 (2H; d; J = 8,1 Hz), 7,20 (2H; d; J = 7,7 Hz); 7,69 (1H; s).

2) El dihidrocloruro de 3-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxamida (253 mg, rendimiento 87%) fue obtenido como un sólido blanco del terc-butilo {[5-({[4-(aminocarbonil)-1-metil-1H-pirazol-3-il]oxi}metil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (307 mg; 0,588 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,14-2,27 (1H;

m); 2,38 (3H; s); 2,93 (3H; brs); 3,17 (2H; brs); 3,63 (3H; s); 3,82 (2H; d; J = 4,7 Hz); 4,93 (2H; s); 6,37 (1H; brs); 7,08 (1H; brs); 7,29 (2H; d; J = 7,9 Hz); 7,35 (2H; d; J = 8,1 Hz); 7,91 (1H; s); 8,42 (3H, brs).

Ejemplo 308

dihidrocloruro de ácido (3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-il)acético

1) A una solución de terc-butilo {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,00 g; 2,51 mmol), metil (3-hidroxi-1-metil-1H-pirazol-4-il)acetato (0,43 g; 2,51 mmol) y tributilfosfina (0,61 g; 3,01 mmol) en tetrahidrofurano (20 mL) fue agregado 1,1'-(azodicarbonil)dipiperidine (0,76 g; 3,01 mmol) y la mezcla fue agitada a la temperatura ambiente por 30 min. La mezcla de reacción fue filtrada y el solvente en el filtrado fue evaporado bajo presión reducida. El residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar metil (3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-il)acetato (1,20 g; rendimiento 86%) como un aceite incoloro. Entonces, fue obtenido ácido (3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-il)acético (173 mg, rendimiento 15%) como un sólido blanco de

metil (3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-il)acetato (1,20 g; 2.18 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,95 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,12-2,30 (1H; m); 2,36 (3H; s); 2,62 (3H; s); 2,80 (2H; d; J = 7,2 Hz); 3,35 (2H; s); 3,66 (3H; s); 4,05-4,09 (2H; m); 4,27 (1H; brs); 4,84 (2H; s); 7,03 (2H; d; J = 7,9 Hz); 7,12 (1H; s); 7,18 (2H; d; J = 7,7 Hz).

2) El dihidrocloruro de ácido (3-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-il)acético (84,2 mg; rendimiento 51%) fue obtenido como un sólido blanco de ácido (3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-il)acético (173 mg; 0,323 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,16-2,27 (1H; m); 2,38 (3H; s); 2,76 (3H; brs); 3,00 (2H; brs); 3,15 (2H; s); 3,58 (3H; s); 3,77-3,84 (2H; m); 4,76 (2H; s); 7,23 (2H; d; J = 7,7 Hz); 7,33 (2H; d; J = 7,5 Hz); 7,37 (1H; s); 8,18 (3H, brs).

Ejemplo 309

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-

metilfenil)piridin-3-il]-3-(1H-tetrazol-5-il)benzamida

A una solución de terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (383 mg; 1,0 mmol) en tetrahidrofurano (5 mL) fue agregado cloruro de 3-cianobenzoilo (245 mg; 1,5 mmol) y fue agregado trietilamina (280 mL; 2,0 mmol). La mezcla fue agitada durante 18 horas. Fue agregada solución acuosa saturada de carbonato hidrógeno de sodio (5 mL) a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar un aceite. A una solución del aceite obtenido en dimetilsulfóxido (3 mL) fue agregada azida de sodio (97 mg; 1,5 mmol) y cloruro de amonio (312 mg; 2,0 mmol) y la mezcla fue agitada a 100? para 3 hr. El agua destilada (10 mL) fue agregada a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar un aceite. A una solución del aceite obtenido en el acetato de etilo (2 mL) fue agregada una solución 4N de ácido clorhídrico acetato de etilo (2 mL) y la mezcla resultante

fue agitada a temperatura ambiente por 3 hr. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue cristalizado del hexano para dar dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-3-(1H-tetrazol-5-il)benzamida (86 mg, rendimiento 16%) como un polvo blanco.

^{1}H-RMN (DOSO-d_6)δ:0,99 (6H; d; J = 6,6 Hz); 2,11-2,27 (1H; m); 2,27 (3H; s); 2,52 (3H; s); 2,93 (2H; s); 3,83 (2H; s); 7,22 (4H; s); 7,64 (1H; t; J = 7,8 Hz); 7,76 (1H; d; J = 7,8 Hz); 8,16 (4H; brs); 8,34 (1H; brs); 10,10 (1H; brs).

Ejemplo 310

Dihidrocloruro de metil 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metilbenzoato

1) El metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metilbenzoato (600 mg, rendimiento 44%) fue obtenido como polvo blanco del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,0 g; 2,51 mmol) y metil 2-hidroxi-3-metilbenzoato (500 mg; 3,01 mmol) según un método similar al método del Ejemplo 214-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 1,80 (3H; s); 2,15-2,28 (1H; m); 2,34 (3H; s); 2,70 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,66 (3H; s); 3,97 (2H; d; J = 4,9 Hz); 4,20 (1H; brs); 4,76 (2H; s); 6,52 (2H; d; J = 7,9 Hz); 6,99

(2H; d; J = 7,9 Hz); 7,01-7,06 (1H; m); 7,19 (1H; dd; J = 7,4; 1,0 Hz); 7,44 (1H; dd; J = 7,7; 1,0 Hz).

2) El dihidrocloruro de metil 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metilbenzoato (215 mg, rendimiento 94%) fue obtenido como polvo blanco de metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metilbenzoato (240 mg; 0,439 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:1,01 (6H; d; J = 6,4 Hz); 1,82 (3H; s); 2,14-2,29 (1H; m); 2,36 (3H; s); 3,02 (3H; s); 3,31 (2H; d; J = 6,8 Hz); 3,67 (3H; s); 3,78 (2H; d; J = 2,45 Hz); 4,81 (2H; s); 6,89 (2H; d; J = 7,7 Hz); 7,11-7,20 (3H; m); 7,33 (1H; d; J = 7,0 Hz); 7,43 (1H; d; J = 7,0 Hz); 8,63 (3H; brs).

Ejemplo 311

Dihidrocloruro de 2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-N-ciclopropilacetamida

1) Una mezcla de ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acético (200 mg; 0,469 mmol), ciclopropilamina (80 mg; 1,41 mmol), 1-hidroxi-1H-benzotriazol (215 mg; 1,41 mmol), hidrocloruro de 1-etil-3-(3-dimetilaminopropil)carbodiimida (270 mg; 0,65 mmol) y N,N-dimetilformamida (5 mL) fue agitado a temperatura ambiente

por 16 hrs. La mezcla de reacción fue diluída con acetato de etilo y fue lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio y el solvente fue evaporado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice para dar terc-butil {[5-[2-(ciclopropilamino)-2-oxoetil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (150 mg, rendimiento 69%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,33-0,39 (2H; m); 0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 1,80 (3H; s); 2,13-2,29 (1H; m); 2,40 (3H; s); 2,54 (3H; s); 2,57-2,64 (1H; m); 2,75 (2H; d; J = 7,4 Hz); 3,23 (2H; s); 4,05 (2H; s); 4,20 (1H; brs); 6,94 (2H; d; J = 7,9 Hz); 7,23 (2H; d; J = 7,9 Hz).

2) El dihidrocloruro de 2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-N-ciclopropilacetamida (100 mg, rendimiento 89%) fue obtenido como polvo blanco del terc-butil {[5-[2-(ciclopropilamino)-2-oxoetil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (120 mg; 0,258 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,34 (2H; s); 0,57 (2H; d; J = 5,5 Hz); 0,99 (6H; d; J = 6,2 Hz); 2,11-2,25 (1H; m); 2,41 (3H; s); 2,53-2,58 (1H; m); 2,81 (2H; s); 3,24 (2H; s); 3,6-3,9 (5H; m); 7,20 (2H; d; J = 7,7 Hz); 7,37 (2H; d; J = 7,7 Hz); 8,08 (1H;

d; J = 3,4 Hz); 8,56 (3H; brs).

Ejemplo 312

Dihidrocloruro de {[2-isobutil-6-metil-4-(4-metilfenil)-5-(2-morfolin-4-il-2-oxoetil)piridin-3-il]metil}amina

1) Terc-butil {[2-isobutil-6-metil-4-(4-metilfenil)-5-(2-morfolin-4-il-2-oxoetil)piridin-3-il]metil}carbamato (50 mg, rendimiento 22%) fue obtenido como polvo blanco de ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acético (200 mg; 0,469 mmol) y tetrahidrooxazina (123 mg; 1,41 mmol) según un método similar al método del Ejemplo 311-1)..

^{1}H-RMN ($CDCl_3$) δ: 0,97 (6H; d; J = 6,6 Hz); 1,37 (9H; s); 2,09-2,27 (1H; m); 2,41 (3H; s); 2,50 (3H; s); 2,73 (2H; d; J = 7,4 Hz); 3,17 (2H; d; J = 4,1 Hz); 3,30 (2H; s); 3,41 (2H; d; J = 4,1 Hz); 3,56 (4H; dd; J = 16,5; 4,1 Hz); 4,04 (2H; d; J = 4,52 Hz); 4,20 (1H; brs); 6,98 (2H; d; J = 7,9 Hz); 7,22 (2H; d; J = 7,9 Hz).

2) El dihidrocloruro de {[2-isobutil-6-metil-4-(4-metilfenil)-5-(2-morfolin-4-il-2-oxoetil)piridin-3-il]metil}amina (40 mg, rendimiento 94%) fue obtenido como polvo blanco del terc-butil {[2-isobutil-6-metil-4-(4-metilfenil)-5-(2-morfolin-4-il-2-oxoetil)piridin-3-il]metil}carbamato (45 mg; 0,0908 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,4 Hz); 2,09-2,30 (1H; m);

2,41 (3H; s); 2,50 (3H; s); 2,79 (2H; s); 3,09-3,42 (10H; m); 3,82 (2H; d; J = 3,8 Hz); 7,16 (2H; d; J = 7,7 Hz); 7,39 (2H; d; J = 7,7 Hz); 8,52 (3H; brs).

Ejemplo 313

Dihidrocloruro de 2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-N-bencilacetamida

1) Terc-butil {[5-[2-(bencilamino)-2-oxoetil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (150 mg, rendimiento 62%) fue obtenido como polvo blanco de ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acético (200 mg; 0,469 mmol) y bencilamina (151 mg; 1,41 mmol) según un método similar al método del Ejemplo 311-1).

^{1}H-RMN ($CDCl_3$) δ: 0,96 (6H; d; J = 6,6 Hz); 1,37 (9H; s); 2,12-2,27 (1H; m); 2,37 (3H; s); 2,56 (3H; s); 2,74 (2H; d; J = 7,2 Hz); 3,32 (2H; s); 4,02 (2H; d; J = 5,1 Hz); 4,20 (1H; brs); 4,34 (2H; d; J = 5,8 Hz); 5,45 (1H; brs); 6,88 (2H; d; J = 7,9 Hz); 7,10-7,20 (4H; m); 7,25-7,35 (3H; m).

2) El dihidrocloruro de 2-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-N-bencilacetamida (125 mg, rendimiento 100%) fue obtenido como polvo blanco del terc-butil {[5-[2-(bencilamino)-2-oxoetil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (130 mg; 0,252 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,4 Hz); 2,07-2,28 (1H; m); 2,40 (3H; s); 2,83 (3H; s); 3,28 (2H; d; J = 7,0 Hz); 3,42 (2H s); 3,81 (2H; d; J = 3,0 Hz); 4,21 (2H; d; J = 5,7 Hz); 7,10-7,44 (9H; m); 8,52 (3H; brs).

Ejemplo 314

Dihidrocloruro de [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(1H-tetrazol-5-il)fenoxi]metil}piridin-3-il)metil]amina

1) El Terc-butil {[5-[(2-cianofenoxi)metil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (586 mg, rendimiento 70%) fue obtenido como un aceite incoloro del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,67 g; 1,68 mmol) y 2-hydroxybenzonitrile (221 mg; 1,85 mmol) según un método similar al método del Ejemplo 214-1),

^{1}H-RMN ($CDCl_3$) δ:1,00 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,19-2,28 (1H; m); 2,34 (3H; s); 2,66 (3H; s); 2,79 (2H; d; J = 7,2 Hz); 4,09-4,11 (2H; m); 4,26 (1H; brs); 4,73 (2H; s); 6,76 (1H; d; J = 8,5 Hz); 6,96-7,01 (2H; m); 7,09 (2H; d; J = 8,1 Hz); 7,18 (2H; d; J = 7,9 Hz); 7,40-7,46 (1H; m); 7,50-7,56 (1H; m).

2) Terc-butil [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(1H-tetrazol-5-il)fenoxi]metil}piridin-3-il)metil]carbamato (400 mg, rendimiento 63%) fue obtenido como un sólido blanco del terc-butil {[5-[(2-cianofenoxi)metil]-2-isobutil-6-metil-

4-(4-metilfenil)piridin-3-il]metil}carbamato (586 mg; 1,17 mmol) según un método similar al método del Ejemplo 251-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,17-2,28 (1H; m); 2,32 (3H; s); 2,59 (3H; s); 2,82 (2H; d; J = 7,4 Hz); 4,09-4,13 (2H; m); 4,31 (1H; brs); 4,92 (2H; s); 6,91-6,95 (3H; m); 7,12 (2H; d; J = 7,7 Hz); 7,18 (1H; t; J = 7,6 Hz); 7,43-7,49 (1H; m); 8,42 (2H; dd; J = 7,9; 1,7 Hz).

3) El dihidrocloruro de [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(1H-tetrazol-5-il)fenoxi]metil}piridin-3-il)metil]amina (327 mg, rendimiento 86%) fue obtenido como un sólido blanco del terc-butil [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[2-(1H-tetrazol-5-il)fenoxi]metil}piridin-3-il)metil]carbamato (400 mg; 0,737 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,01 (6H; d; J = 6,6 Hz); 2,17-2,29 (4H; m); 2,88 (3H; brs); 3,16 (2H; brs); 3,80 (2H; brs); 4,89 (2H; s); 7,03-7,10 (3H; m); 7,13-7,17 (3H; m); 7,46-7,52 (1H; m); 7,87 (1H; d; J = 7,7 Hz); 8,41 (3H; brs).

Ejemplo 315

Dihidrocloruro de 5-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilen}-1,3-tiazolidin-2,4-diona

1) Una mezcla de terc-butil {[5-formil-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (600 mg; 1,51 mmol), 1,3-tiazolidin-2,4-diona (177 mg, 1,51 mmol),

piperidina (0,015 mL) y etanol (10 mL) fue agitada con calentamiento a 80°C durante 3,5 días. Después de permitir que se enfríe a la temperatura ambiente, el solvente fue evaporado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice para dar terc-butil {[5-[(2,4-dioxo-1,3-tiazolidin-5-iliden)metil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (400 mg, rendimiento 53%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,12-2,31 (1H; m); 2,38 (3H; s); 2,50 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 4,12 (2H; d; J = 5,1 Hz); 4,20 (1H; brs); 6,96 (2H; d; J = 8,1 Hz); 7,19 (2H; d; J = 8,1 Hz); 7,51 (1H; s).

2) El dihidrocloruro de 5-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilen}-1,3-tiazolidin-2,4-diona (155 mg, rendimiento 100%) fue obtenido como polvo blanco del terc-butil {[5-[(2,4-dioxo-1,3-tiazolidin-5-iliden)metil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (157 mg; 0,316 mmol) según un método similar al método del Ejemplo 2-3).

1H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,4 Hz); 2,14-2,29 (1H; m); 2,37 (3H; s); 2,51 (3H; s); 3,08 (2H; d; J = 6,4 Hz); 3,83 (2H; d; J = 4,7 Hz); 7,23 (2H; d; J = 8,1 Hz); 7,28-7,40 (3H; m); 8,49 (3H; brs).

Ejemplo 316

Dihidrocloruro de ácido 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metilbenzoico

1) El ácido 2-{[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metilbenzoico (280 mg, rendimiento 93%) fue obtenido como polvo blanco de metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metilbenzoato (300 mg; 0,563 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:1,07 (6H; d; J = 6,4 Hz); 1,38 (9H; s); 1,96 (3H; s); 2,24-2,32 (1H; m); 2,36 (3H; s); 3,14 (3H; s); 3,31 (2H; d; J = 6,8 Hz); 4,06 (2H; d; J = 4,3 Hz); 4,20 (1H; brs); 4,83 (2H; s); 6,60 (2H; d; J = 7,5 Hz); 7,02-7,13 (3H; m); 7,19-7,24 (1H; m); 7,45-7,54 (1H; m).

2) El dihidrocloruro de ácido 2-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metilbenzoico (55 mg, rendimiento 100%) fue obtenido como polvo blanco del ácido 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metilbenzoico (58,4 mg; 0,110 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,4 Hz); 1,79 (3H; s);

2,14-2,28 (1H; m); 2,36 (3H; s); 2,97 (3H; s); 3,26 (2H; d; J = 6,8 Hz); 3,77 (2H; d; J = 4,0 Hz); 4,81 (2H; s); 6,93 (2H; d; J = 7,9 Hz); 7,09 (1H; t; J = 7,5 Hz); 7,19 (2H; d; J = 7,9 Hz), 7,29 (1H; d; J = 6,6 Hz); 7,38-7,46 (1H; m); 8,57 (3H; brs).

Ejemplo 317

Dihidrocloruro de 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-clorobenzamida

1) El ácido 2-{[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-clorobenzoico (0,54 g; rendimiento 97%) fue obtenido como polvo blanco del metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-clorobenzoato (0,57 g; 1,0 mmol) según un método similar al método del Ejemplo 43-1).

^{1}H-RMN ($CDCl_3$)δ: 1,04 (6H; d; J = 6,6 Hz); 1,37 (9H; s); 2,20-2,35 (1H; m); 2,40 (3H; s); 3,00 (3H; s); 3,21 (2H; d; J = 5,2 Hz); 4,17 (2H; d; J = 5,8 Hz); 4,50-4,65 (1H; m); 4,88 (2H; s); 6,62 (1H; d; J = 8,9 Hz); 7,05 (2H; d; J = 7,8 Hz); 7,25 (2H; d; J = 7,8 Hz); 7,33 (1H; dd; J = 2,6; 8,9 Hz); 7,90 (1H; d; J = 8,9 Hz).

2) Terc-butil {[5-{[2-(aminocarbonil)-4-clorofenoxi]metil}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,20 g; rendimiento 71%) fue obtenido como polvo blanco de ácido 2-{[5-{[(terc-

butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-clorobenzoico (0,28 g; 0,51 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$)δ: 0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,15-2,35 (1H; m); 2,36 (3H; s); 2,63 (3H; s); 2,80 (2H; d; J = 7,4 Hz); 4,10 (2H; d; J = 5,1 Hz); 4,15-4,30 (1H; m); 4,77 (2H; s); 5,65 (1H; brs); 6,69 (1H; d; J = 8,9 Hz); 6,99 (2H; d; J = 7,9 Hz); 7,18 (2H; d; J = 7,9 Hz); 7,31 (1H; dd; J = 2,8; 8,9 Hz); 7,48 (1H; brs); 8,18 (1H; d; J = 2,8 Hz).

3) El dihidrocloruro de 2-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-clorobenzamida (0,16 g; rendimiento 99%) fue obtenido como polvo blanco del terc-butil {[5-{[2-(aminocarbonil)-4-clorofenoxi]metil}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,17 g; 0,31 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,6 Hz); 2,15-2,35 (1H; m); 2,36 (3H; s); 2,84 (3H; brs); 3,08 (2H; brs); 3,82 (2H; d; J = 2,6 Hz); 4,79 (2H; s); 6,83 (1H; d; J = 9,0 Hz); 7,25 (2H; d; J = 7,9 Hz); 7,31 (2H; d; J = 7,9 Hz); 7,41 (1H; dd; J = 2,7; 9,0 Hz); 7,52 (2H; brs); 7,55 (1H; d; J = 2,7 Hz); 8,36 (3H; brs).

Ejemplo 318

Dihidrocloruro de ácido 2-{[5-(aminometil)-6-isobutil-2-

metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-clorobenzoico

El dihidrocloruro de ácido 2-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-clorobenzoico (0.16 g; rendimiento 85%) fue obtenido como polvo blanco de ácido 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-5-clorobenzoico (0,20 g; 0,36 mmol) según un método similar al método del Ejemplo 276-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,6 Hz); 2,15-2,30 (1H; m); 2,36 (3H; s); 2,83 (3H; brs); 3,05 (2H; brs); 3,75-3,90 (2H; m); 4,77 (2H; brs); 6,92 (1H; d; J = 8,9 Hz); 7,24 (2H; d; J = 7,8 Hz); 7,31 (2H; d; J = 7,8 Hz); 7,47 (1H; dd; J = 2,8; 8,9 Hz); 7,61 (1H; d; J = 2,8 Hz); 8,30 (3H; brs).

Ejemplo 319

Dihidrocloruro de ácido 4'-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]bifenil-4-carboxílico

1) 4-Bromobencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,92 g; rendimiento 75%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,82 g; 4,41 mmol) y bromuro de 4-bromobencilo (1,10 g; 4,41 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,15-

2,26 (1H; m); 2,38 (3H; s); 2,53 (3H; s); 2,77 (2H; d; J = 7,2 Hz); 4,11 (2H; d; J = 4,9 Hz); 4,19 (1H; brs); 4,89 (2H; s); 6,91 (2H; d; J = 8,5 Hz); 6,99 (2H; d; J = 8,1 Hz); 7,09 (2H; d; J = 7,7 Hz); 7,39 (2H; d; J = 8,5 Hz).

2) Una solución de 4-bromobencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,09 g; 1,87 mmol), ácido [4-(metoxicarbonil)fenil]borónico (675 mg; 3,75 mmol), carbonato de potasio (388 mg; 2,81 mmol) y tetrakis(trifenilfosfina)paladio(0) (216 mg; 0,187 mmol) en dioxano (15 mL) y agua (2,5 mL) fueron agitados bajo atmósfera de argón por 12 hrs. La mezcla de reacción fue diluída con acetato de etilo, fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar [4'-(metoxicarbonil)bifenil-4-il]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (570 mg, rendimiento 48%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,17-2,26 (1H; m); 2,29 (3H; s); 2,55 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 3,91 (3H; s); 4,16 (2H; d; J = 4,5 Hz); 4,60 (1H; brs); 4,98 (2H; s); 7,07 (2H; d; J = 8,1 Hz); 7,12-7,16 (4H; m); 7,53 (2H; d; J = 8,3 Hz); 7,64 (2H; d; J = 8,7 Hz); 8,10

(2H; d; J = 8,5 Hz).

3) El ácido 4'-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]bifenil-4-carboxílico (380 mg, rendimiento 68%) fue obtenido como un sólido blanco de [4'-(metoxicarbonil)bifenil-4-il]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (570 mg; 0,895 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,15-2,26 (1H; m); 2,34 (3H; s); 2,56 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 4,11-4,16 (2H; m); 4,23 (1H; brs); 4,99 (2H; s); 7,05 (2H; d; J = 7,9 Hz); 7,13-7,18 (4H; m); 7,55 (2H; d; J = 8,3 Hz); 7,68 (2H; d; J = 8,5 Hz); 8,18 (2H; d; J = 8,3 Hz).

4) Dihidrocloruro de ácido 4'-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]bifenil-4-carboxílico (255 mg, rendimiento 70%) fue obtenido como un sólido blanco del ácido 4'-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]bifenil-4-carboxílico (380 mg; 0,610 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,15-2,26 (1H; m); 2,33 (3H; s); 2,57 (3H; brs); 2,92 (2H; brs); 3,82 (2H;

d; J = 4,3 Hz); 5,04 (2H; s); 7,18 (4H; d; J = 8,3 Hz); 7,24 (2H; d; J = 8,1 Hz); 7,68 (2H; d; J = 8,3 Hz); 7,82 (2H; d; J = 8,5 Hz); 8,04 (2H; d; J = 8,5 Hz); 8,34 (3H; brs).

Ejemplo 320

trihidrocloruro de piridin-4-ilmetil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) Piridin-4-ilmetil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (322 mg, rendimiento 53%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (0,50 g; 1,21 mmol), hidrocloruro de 4-(clorometil)piridina (0;20 g; 1,21 mmol) y carbonato de potasio (0,42 g; 3,0 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$)d:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,17-2,27 (1H; m); 2,36 (3H; s); 2,56 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 4,14 (2H; d; J = 4,9 Hz); 4,42 (1H; brs); 4,94 (2H; s); 6,89 (2H; d; J = 5,8 Hz); 7,04 (2H; d; J = 8,1 Hz); 7,12 (2H; d; J = 7,9 Hz); 8,48 (2H; d; J = 5,3 Hz).

2) El trihidrocloruro de Piridin-4-ilmetil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (260 mg, rendimiento 79%) fue obtenido como un sólido blanco del piridin-4-ilmetil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (322 mg; 0,639 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,19-2,27 (1H; m); 2,33 (3H; s); 2,57 (3H; brs); 2,89 (2H; brs); 3,81 (2H; d; J = 5,5 Hz); 5,29 (2H; s); 7,17-7,24 (4H; m); 7,60 (2H; brs); 8,35 (3H; brs); 8,83-8,84 (2H; brs).

Ejemplo 321

El trihidrocloruro de piridin-3-ilmetil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) El piridin-3-ilmetil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (454 mg, rendimiento 74%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (0,50 g; 1,21 mmol), hidrobromuro de 3-(bromometil)piridina (0,46 g; 1,81 mmol) y carbonato de potasio (0,50 g; 3,6 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$)δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,15-2,24 (1H; m); 2,36 (3H; s); 2,54 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 4,12 (2H; d; J = 4,1 Hz); 4,20 (1H; brs); 4,94 (2H; s); 6,99 (2H; d; J = 8,1 Hz); 7,09 (2H; d; J = 7,9 Hz); 7,17-7,21 (1H; m); 7,32-7,37 (1H; m); 8,34 (1H; d; J = 1,7 Hz); 8,55 (1H; dd; J = 4,8; 1,6 Hz).

2) El trihidrocloruro de piridin-3-ilmetil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (183 mg,

rendimiento 39%) fue obtenido como un sólido blanco del piridin-3-ilmetil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (454 mg; 0,903 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,8 Hz); 2,17-2,26 (1H; m); 2,31 (3H; s); 2,59 (3H; s); 2,93 (2H; d; J = 6,0 Hz); 3,78 (2H; d; J = 5,5 Hz); 5,22 (2H; s); 7,12 (4H; s); 7,95 (1H; t; J = 6,7 Hz); 8,14 (1H; d; J = 7,9 Hz); 8,41 (3H; brs); 8,67 (1H; s); 8,90 (1H; d; J = 5,5 Hz).

Ejemplo 322

Dihidrocloruro de metil 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metoxibenzoato

1) metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metoxibenzoato (0,62 g; rendimiento 55%) fue obtenido como polvo blanco del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,80 g; 2,0 mmol) y metil 3-metoxisalicilato (0,55 g; 3,0 mmol) según un método similar al método del Ejemplo 106-1).

^{1}H-RMN ($CDCl_3$)δ: 0,98 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,15-2,30 (1H; m); 2,34 (3H; s); 2,73 (3H; s); 2,75 (2H; d; J = 7,4 Hz); 3,54 (3H; s); 3,64 (3H; s); 3,97 (2H; d; J = 5,1 Hz); 4,20-4,30 (1H; m); 4,86 (2H; s); 6,60 (2H; d; J = 8,1 Hz); 6,85 (1H; dd; J = 1,5; 8,1 Hz); 7,01 (2H; d; J = 8,1

Hz); 7,06 (1H; d; J = 8,1 Hz); 7,14 (1H; dd; J = 1,5; 8,1 Hz).

2) El dihidrocloruro de metil 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metoxibenzoato (0.12 g; rendimiento 66%) fue obtenido como polvo blanco de metil 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metoxibenzoato (0,19 g; 0,34 mmol) según un método similar al método del Ejemplo 274-2).

^{1}H-RMN (DMSO-d_6)δ: 0,99 (6H; d; J = 6,6 Hz); 2,10-2,30 (1H; m); 2,37 (3H; s); 2,94 (3H; brs); 3,00-3,20 (2H; m); 3,51 (3H; s); 3,63 (3H; s); 3,72 (2H; brs); 4,88 (2H; brs); 6,77 (2H; d; J = 7,9 Hz); 7,00-7,22 (3H; m); 7,17 (2H; d; J = 7,9 Hz), 8,27 (3H; brs).

Ejemplo 323

Dihidrocloruro de metil 2-({[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metil}tio)benzoato

1) El metil 2-({[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metil}tio)benzoato (1,46 g; rendimiento 63%) fue obtenido como polvo de metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metilo (2,0 g; 4,7 mmol) y tiosalicilato de metilo (757 mg, 45 mmol) según un método

similar al método del Ejemplo 33-1).

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,37 (9H; s); 2,34 (3H; s); 2,65 (3H; s); 2,83 (2H; s); 3,89 (3H; s); 4,07 (2H; d; J=4,9 Hz); 4,17 (1H; brs); 7,04-7,18 (6H; m); 7,32-7,38 (1H; m); 7,91-7,95 (1H; m).

2) El dihidrocloruro de metil 2-({[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metil}tio)benzoato (254 mg, rendimiento 89%) fue obtenido como polvo de metil 2-({[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metil}tio)benzoato (300 mg; 0,533 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,03 (9H; s); 2,34 (3H; s); 2,83 (3H; s); 3,18 (2H; brs); 3,80 (3H; s); 3,88 (2H; s); 4,00 (2H; s); 7,23-7,32 (6H; m); 7,47-7,52 (1H; m); 7,85-7,88 (1H; m); 8,21 (3H; brs).

Ejemplo 324

Dihidrocloruro de ácido 2-({[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metil}tio)benzoico

1) El ácido 4-({[5-{[(terc-Butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metil}tio)benzoico (897 mg, rendimiento 92%) fue obtenido como un sólido blanco de metil 4-({[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-

neopentilpiridin-3-il]metil}tio)benzoato (1,0 g; 1,78 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:1,12 (9H; s); 1,38 (9H; s); 2,38 (3H; s); 3,09 (3H; s); 3,47 (2H; s); 3,79 (2H; s); 4,14 (2H; d; J=4,3 Hz); 4,52 (1H; brs); 6,85-6,92 (2H; m); 7,08-7,13 (1H; m); 7,19-7,21 (2H; m); 7,29-7,33 (1H; m); 7,37-7,41 (1H; m); 7,94-7,97 (1H; m).

2) El dihidrocloruro de ácido 2-({[5-(Aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metil}tio)benzoico (158 mg, rendimiento 83%) fue obtenido como polvo blanco de ácido 4-({[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metil}tio)benzoico (200 mg; 0,364 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,03 (9H; s); 2,34 (3H; s); 2,81 (3H; s); 3,15 (2H; brs); 3,80 (2H; s); 3,85 (2H; s); 7,19-7,33 (6H; m); 7,44-7,49 (1H; m); 7,86-7,89 (1H; m); 8,17 (3H; brs).

Ejemplo 325

Dihidrocloruro de 2-({[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metil}tio)benzamida

1) 4-({[5-{[(terc-Butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metil}tio)benzamida (349 mg, rendimiento 70%) fue obtenido como un sólido blanco de ácido 4-({[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-

(4-metilfenil)-6-neopentilpiridin-3-il]metil}tio)benzoico (500 mg; 0,911 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,37 (9H; s); 2,39 (3H; s); 2,63 (3H; s); 2,83 (2H; s); 3,81 (2H; s); 4,04 (2H; d; J=5,1 Hz); 4,24 (1H; brs); 5,45 (1H; brs); 6,68 (1H; brs); 6,96-6,99 (2H; m); 7,18-7,22 (3H; m); 7,28-7,32 (2H; m); 7,75-7,78 (1H, m).

2) El dihidrocloruro de 2-({[5-(Aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metil}tio)benzamide (160 mg, rendimiento 84%) fue obtenido como polvo blanco de 4-({[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metil}tio)benzamida (200 mg; 0,365 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,03 (9H; s); 2,37 (3H; s); 2,76 (3H; s); 3,17 (2H; brs); 3,75-3,85 (4H; m); 7,14-7,35 (7H; m); 7,40 (1H; s); 7,50-7,48 (1H; m); 7,81 (1H; s); 8,20 (3H; brs).

Ejemplo 326

Dihidrocloruro de 2-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metilbenzamida

1) El terc-butil {[5-{[2-(aminocarbonil)-6-metilfenoxi]metil}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (190 mg, rendimiento

95%) fue obtenido como polvo blanco del ácido 2-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metilbenzoico (200 mg; 0,375 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:1,05 (6H; d; J = 6,2 Hz); 1,40 (9H; s); 1,93 (3H; s); 2,21-2,32 (1H; m); 2,36 (3H; s); 3,01 (3H; s); 3,16 (2H; d; J = 6,8 Hz); 4,04 (2H; s); 4,20 (1H; brs); 4,81 (2H; s); 5,80 (1H; brs); 6,40 (1H; brs); 6,65 (2H; s); 7,02-7,23 (4H; m); 7,56 (1H; s).

2) El dihidrocloruro de 2-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-3-metilbenzamida (100 mg, rendimiento 70%) fue obtenido como polvo blanco del terc-butil {[5-{[2-(aminocarbonil)-6-metilfenoxi]metil}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (150 mg; 0,282 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,4 Hz); 1,76 (3H; s); 2,13-2,29 (1H; m); 2,37 (3H; s); 2,96 (3H; s); 3,21 (2H; d; J = 6,6 Hz); 3,76 (2H; d; J = 4,9 Hz); 4,78 (2H; s); 7,01 (2H; d; J = 7,9 Hz); 7,04-7,08 (1H; m); 7,15-7,26 (4H; m); 7,34 (1H; brs); 7,53 (1H; brs); 8,52 (3H; brs).

Ejemplo 327

Dihidrocloruro de 2-[5-(aminometil)-6-isobutil-2-metil-4-(4-

metilfenil)piridin-3-il]-N-fenilacetamida

1) El terc-butil {[5-(2-anilino-2-oxoetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (220 mg, rendimiento 94%) fue obtenido como polvo blanco de ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acético (200 mg; 0,469 mmol) y anilina (150 mg; 1,41 mmol) según un método similar al método del Ejemplo 311-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,15-2,29 (1H; m); 2,40 (3H; s); 2,63 (3H; s); 2,77 (2H; d; J = 7,2 Hz); 3,66 (3H; s); 4,06 (2H; d; J = 4,9Hz); 4,20 (1H; brs); 7,02 (2H; d; J = 7,9 Hz); 7,06-7,14 (1H; m); 7,24 (2H; d; J = 7,9 Hz); 7,27-7,39 (4H; m).

2) El dihidrocloruro de 2-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-N-fenilacetamida (200 mg, rendimiento 100%) fue obtenido como polvo blanco del terc-butil {[5-(2-anilino-2-oxoetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (210 mg; 0,419 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:1,00 (6H; d; J = 5,5 Hz); 2,13-2,28 (1H; m); 2,38 (3H; s); 2,85 (3H; s); 3,25 (2H; s); 3,62 (2H; s); 3,83 (2H; s); 7,04 (1H; t; J = 6,7 Hz); 7,15-7,42 (6H; m); 7,50 (2H; d; J = 7,4 Hz); 8,53 (3H; brs); 10,20 (1H; s).

Ejemplo 328

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]ciclohexancarboxamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]ciclohexancarboxamida (230 mg, rendimiento 98%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de ciclohexancarbonilo (100 mL; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 0,98 (6H; d; J = 6,6 Hz); 1,00-1,25 (6H; m); 1,41 (2H; brs); 1,59 (2H; brs); 2,08-2,22 (2H; m); 2,37 (3H; s); 2,53 (3H; s); 3,03 (2H; brs); 3,81 (2H; s); 7,14 (2H; d; J = 7,8 Hz); 7,30 (2H; d; J = 7,8 Hz); 8,33 (3H; brs); 9,37 (1H; brs).

Ejemplo 329

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]piperidin-1-carboxamida

1) Terc-butil ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(piperidin-1-ilcarbonil)amino]piridin-3-il}metil)carbamato fue obtenido como un aceite de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y piperidina (150 µL; 1,5 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):495

2) El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]piperidin-1-carboxamida (218 mg, rendimiento 47%) fue obtenido como polvo blanco del aceite obtenido en 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,98 (6H; d; J = 6,3 Hz); 1,07-1,19 (4H; m); 1,44 (2H; brs); 2,12-2,27 (1H; m); 2,37 (3H; s); 2,60 (3H; s); 3,05 (2H; brs); 3,15 (4H; brs); 3,83 (2H; s); 7,19 (2H; d; J = 7,8 Hz); 7,31 (2H; d; J = 7,8 Hz); 7,96 (1H; brs); 8,27 (3H; brs).

Ejemplo 330

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]tetrahidro-2H-piran-4-carboxamida

Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]tetrahidro-2H-piran-4-carboxamida (232 mg, rendimiento 98%) fue obtenido como polvo blanco del terc-butil ([5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil)carbamato (192 mg; 0,5 mmol) y cloruro de tetrahidro-2H-piran-4-carbonilo (111 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 0,98 (6H; d; J = 6,6 Hz); 1,00-1,25 (6H; m); 1,41 (2H; brs); 1,59 (2H; brs); 2,08-2,22 (2H; m); 2,37 (3H; s); 2,53 (3H; s); 3,03 (2H; brs); 3,81 (2H; s); 7,14

(2H; d; J = 7,5 Hz); 7,30 (2H; d; J = 7,8 Hz); 8,27 (3H; brs); 9,43 (1H; brs).

Ejemplo 331

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]morfolin-4-carboxamida

1) Terc-butil ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(morfolin-4-ilcarbonil)amino]piridin-3-il}metil)carbamato fue obtenido como un aceite de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y tetrahidrooxazina (130 µL; 1,5 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):497

2) El dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]morfolin-4-carboxamida (278 mg, rendimiento 59%) fue obtenido como polvo blanco del aceite obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,3 Hz); 2,10-2,27 (1H; m); 2,39 (3H; s); 2,70 (3H; s); 3,14 (6H; brs); 3,19 (4H; brs); 3,86 (2H; brs); 7,21 (2H; d; J = 7,8 Hz); 7,34 (2H; d; J = 7,8 Hz); 8,44 (4H; brs).

Ejemplo 332

Trihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-

metilfenil)piridin-3-il]piperidin-4-carboxamida

El trihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]piperidin-4-carboxamida (246 mg, rendimiento 98%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y bencil 4-(clorocarbonil)piperidin-1-carboxilato (210 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 0,98 (6H; d; J = 6,6 Hz); 1,44 (4H; brs); 2,15-2,26 (1H; m); 2,38 (3H; s); 2,38-2,57 (1H; m); 2,57 (3H; s); 2,76 (2H; brs); 3,07 (4H; brs); 3,81 (2H; brs); 7,17 (2H; d; J = 8,1 Hz); 7,30 (2H; d; J = 8,1 Hz); 8,41 (3H; brs); 8,80 (1H; brs); 9,09 (1H; brs); 9,84 (1H; brs).

Ejemplo 333

Trihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]piperazin-1-carboxamida

1) Terc-butil 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)piperazin-1-carboxilato fue obtenido como un aceite de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y terc-butil piperazin-1-carboxilato (140 mg; 1,5 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):596

2) El trihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-

metil-4-(4-metilfenil)piridin-3-il]piperazin-1-carboxamida (250 mg, rendimiento 97%) fue obtenido como polvo blanco del aceite obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,98 (6H; d; J = 6,3 Hz); 2,15-2,26 (1H; m); 2,42 (3H; s); 2,62 (2H; s); 2,72 (3H; s); 3,05 (2H; brs); 3,42 (4H; brs); 3,82 (2H; brs); 7,19 (2H; d; J = 7,5 Hz); 7,31 (2H; d; J = 7,5 Hz); 8,37 (3H; brs); 8,60 (1H; brs); 9,41 (2H; brs).

Ejemplo 334

(5-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilen}-4-oxo-2-tioxo-1,3-tiazolidin-3-il)acético dihidrocloruro de ácido

1) El ácido (5-{[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilen}-4-oxo-2-tioxo-1,3-tiazolidin-3-il)acético (355 mg, rendimiento 50%) fue obtenido como polvo amarillo del terc-butilo {[5-formil-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (500 mg; 1,26 mmol) y ácido (4-oxo-2-tioxo-1,3-tiazolidin-3-il)acético (241 mg; 1,26 mmol) según un método similar al método del Ejemplo 315-1).

^{1}H-RMN ($CDCl_3$) δ: 0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,09-2,27 (1H; m); 2,36 (3H; s); 2,50 (3H; s); 2,8 (2H; d; J = 7,4 Hz); 4,01-4,18 (4H; m); 4,20 (1H; brs); 6,96 (2H; d; J

= 7,9 Hz); 7,20 (2H; d; J = 7,9 Hz); 7,38 (1H; s).

2) El dihidrocloruro de ácido (5-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilen}-4-oxo-2-tioxo-1,3-tiazolidin-3-il)acético (198 mg, rendimiento 100%) fue obtenido como polvo amarillo de ácido (5-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilen}-4-oxo-2-tioxo-1,3-tiazolidin-3-il)acético (210 mg; 0,386 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,98 (6H; d; J = 6,4 Hz); 2,17-2,31 (1H; m); 2,36 (3H; s); 2,55 (3H; s); 2,95 (2H; d; J = 6,6 Hz); 3,80 (2H; d; J = 7,4 Hz); 4,63 (2H; s); 7,22 (2H; d; J = 8,1 Hz); 7,30 (2H; d; J = 8,1 Hz); 7,55 (1H; s); 8,35 (3H; brs).

Ejemplo 335

Dihidrocloruro de 5-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il}metilen}-2-tioxo-1,3-tiazolidin-4-ona

1) Terc-butil ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-oxo-2-tioxo-1,3-tiazolidin-5-iliden)metil]piridin-3-il}metil)carbamato (310 mg, rendimiento 48%) fue obtenido como polvo amarillo del terc-butil {[5-formil-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (500 mg; 1,26 mmol) y 2-tioxo-1,3-tiazolidin-4-ona (168 mg; 1,26 mmol) según un método similar al método del Ejemplo 315-1).

^{1}H-RMN ($CDCl_3$) δ: 0,98 (6H; d; J = 6,8 Hz); 1,39 (9H; s);

2,15-2,31 (1H; m); 2,37 (3H; s); 2,50 (3H; s); 2,80 (2H; d; J = 7,4 Hz); 4,13 (2H; d; J = 7,4 Hz); 4,20 (1H; brs); 6,95 (2H; d; J = 7,7 Hz); 7,20 (2H; d; J = 7,7 Hz); 7,34 (1H; s).

2) Un dihidrocloruro de (173 mg, rendimiento 100%) fue obtenido como polvo amarillo del terc-butil ({2-isobutil-6-metil-4-(4-metilfenil)-5-[(4-oxo-2-tioxo-1,3-tiazolidin-5-iliden)metil]piridin-3-il}metil)carbamato (200 mg; 0,390 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,11-2,31 (1H; m); 2,36 (3H; s); 2,52 (2H; s); 2,90 (3H; s); 3,79 (2H; s); 7,19 (2H; d; J = 8,1 Hz); 7,26-7,37 (3H; m); 8,27 (3H; brs).

Ejemplo 336

Dihidrocloruro de metil 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoato

1) Metil 3-({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoato (230 mg, rendimiento 35%) fue obtenido como polvo blanco de ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acético (500 mg; 1,17 mmol) y metil 3-aminobenzoato (532 mg, 3,52 mmol) según un método similar al método del Ejemplo 311-1).

^{1}H-RMN ($CDCl_3$) δ: 0,98 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,16-2,31 (1H; m); 2,41 (3H; s); 2,64 (3H; s); 2,77 (2H; d; J

= 7,4 Hz); 3,47 (2H; s); 3,91 (3H; s); 4,07 (2H; d; J = 4,5 Hz); 4,20 (1H; brs); 5,50 (1H; brs); 7,02 (2H; d; J = 7,9 Hz); 7,24 (2H; d; J = 7,9 Hz); 7,38 (1H; t; J = 7,9 Hz); 7,72-7,86 (3H; m).

2) Dihidrocloruro de metil 3-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoato (65 mg, rendimiento 91%) fue obtenido como polvo blanco de metil 3-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoato (75,2 mg; 0,134 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,98 (6H; d; J = 6,6 Hz); 2,11-2,30 (1H; m); 2,36 (3H; s); 2,53 (3H; s); 2,68 (2H; s); 2,98 (2H; s); 3,78 (2H; s); 3,84 (3H; s); 7,19 (2H; d; J = 8,1 Hz); 7,32 (2H; d; J = 8,1 Hz); 7,44 (1H; t; J = 7,9 Hz); 7,61-7,71 (2H; m); 8,10 (3H; brs); 8,20 (1H; s); 10,6 (1H; brs).

Ejemplo 337

Trihidrocloruro de metil 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)piridin-2-carboxilato

1) El metil 3-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)piridin-2-carboxilato (1,43 g; 2,60 mmol) fue obtenido como un aceite amarillo del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-

il]metil}carbamato (2,08 g; 5,22 mmol) y metil 3-mercaptopiridin-2-carboxilato (883 mg; 5,22 mmol) según un método similar al método del Ejemplo 183-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,14-2,26 (1H; m); 2,35 (3H; s); 2,66 (3H; s); 2,76 (2H; d; J = 7,2 Hz); 3,76 (2H; s); 3,99 (3H; s); 4,03 (2H; d; J = 5,3 Hz); 4,19 (1H; brs); 7,04-7,07 (1H; m); 7,09 (2H; d; J = 8,1 Hz); 7,18 (2H; d; J = 7,7 Hz); 7,28-7,31 (1H; m); 7,40-7,44 (1H; m); 8,43 (1H; dd; J = 4,5; 1,5 Hz).

2) El trihidrocloruro de metil 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)piridin-2-carboxilato (161 mg, rendimiento 80%) fue obtenido como un sólido amarillo pálido de metil 3-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)piridin-2-carboxilato (197 mg; 0,359 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,4 Hz); 2,15-2,26 (1H; m); 2,35 (3H; s); 2,89 (3H; brs); 3,18 (2H; brs); 3,77 (2H; d; J = 5,1 Hz); 3,83 (3H; s); 3,94 (2H; s); 7,25 (2H; d; J = 7,9 Hz); 7,31 (2H; d; J = 8,1 Hz); 7,51 (1H; dd; J = 8,3; 4,5 Hz); 7,76 (1H; d; J = 8,1 Hz); 8,35-8,53 (4H; m).

Ejemplo 338

Trihidrocloruro de ácido 3-({[5-(aminometil)-6-isobutil-2-

metil-4-(4-metilfenil)piridin-3-il]metil}tio)piridin-2-carboxílico

1) El ácido 3-({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)piridin-2-carboxílico (1,19 g; rendimiento 99%) fue obtenido como un aceite incoloro de metil 3-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)piridin-2-carboxilato (1,23 g; 2,24 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:1,06 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,21-2,32 (1H; m); 2,37 (3H; s); 2,97 (3H; brs); 3,17 (2H; brs); 3,81 (2H; s); 4,08-4,13 (2H; m); 4,31 (1H; brs); 7,14 (2H; d; J = 7,9 Hz); 7,24 (2H; d; J = 8,3 Hz); 7,42-7,46 (1H; m); 7,50-7,53 (1H; m); 8,35 (1H; dd; J = 4,4; 1,2 Hz).

2) El trihidrocloruro de ácido 3-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)piridin-2-carboxílico (265 mg, rendimiento 69%) fue obtenido como un sólido amarillo pálido del ácido 3-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)piridin-2-carboxílico (0,38 g; 0,709 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,13-2,24 (1H;

m); 2,34 (3H; s); 2,79-2,82 (3H; m); 3,05 (2H; brs); 3,75 (2H; brs); 3,89 (2H; brs); 7,26 (2H; d; J = 6,4 Hz); 7,31 (2H; d; J = 8,3 Hz); 7,48 (1H; dd; J = 8,3; 4,5 Hz); 7,72 (1H; d; J = 8,3 Hz); 8,19-8,36 (3H; m); 8,43 (1H; d; J = 4,5 Hz).

Ejemplo 339

Trihidrocloruro de 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)piridin-2-carboxamida

1) El terc-butil {[5-({[2-(aminocarbonil)piridin-3-il]tio}metil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (720 mg, rendimiento 88%) fue obtenido como un aceite incoloro del ácido 3-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)piridin-2-carboxílico (0,82 g; 1,53 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,14-2,26 (1H; m); 2,33 (3H; s); 2,67 (3H; s); 2,75 (2H; d; J = 7,2 Hz); 3,71 (2H; s); 4,03 (2H; d; J = 4,9 Hz); 4,18 (1H; brs); 5,44 (1H; brs); 7,12-7,18 (4H; m); 7,25-7,29 (1H; m); 7,42 (1H; dd; J = 8,3; 1,3 Hz); 7,82 (1H; brs); 8,24 (1H; dd; J = 4,3; 1,3 Hz).

2) El trihidrocloruro de 3-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metil}tio)piridin-2-carboxamida (546 mg, rendimiento 74%) fue obtenido como un

sólido amarillo pálido del terc-butil {[5-({[2-(aminocarbonil)piridin-3-il]tio}metil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (720 mg; 1,35 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,01 (6H; d; J = 6,6 Hz); 2,13-2,26 (1H; m); 2,34 (3H; s); 2,96 (3H; s); 3,25 (2H; brs); 3,79 (2H; d; J = 5,1 Hz); 3,86 (2H; s); 7,29-7,40 (4H; m); 7,46 (1H; dd; J = 8,1; 4,5 Hz); 7,64 (1H; brs); 7,69 (1H; d; J = 7,5 Hz); 8,09 (1H; brs); 8,36 (1H; dd; J = 4,5; 1,2 Hz); 8,51 (3H; brs).

Ejemplo 340

Dihidrocloruro de ácido 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]ciclohexancarboxílico

1) Una mezcla de metilo 4-(hidroximetil)ciclohexancarboxilato (0,40 g; 2,32 mmol), trietilamina (0,65 mL; 4,64 mmol) y tetrahidrofurano (10 mL) fue enfriada a 0°C y fue agregado cloruro de metansulfonilo (0,27 mL; 3,48 mmol) por gotas. Después de agitar a temperatura ambiente por 30 min., la mezcla de reacción fue vertida en carbonato de hidrógeno de sodio acuoso saturado, y la mezcla se extrajo con acetato de etilo. El extracto fue secado sobre sulfato de magnesio anhidro y el solvente fue evaporado bajo presión reducida para dar metil 4-{[(metilsulfonil)oxi]metil}ciclohexancarboxilato como un

producto en bruto. El producto en bruto fue disuelto en N,N-dimetilformamida (15 mL), y carbonato de potasio (480 mg; 3,48 mmol) y fue agregado ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (0,95 g; 2,32 mmol). La mezcla fue agitada con calentamiento a 70°C por 1 hr. La mezcla de reacción fue diluida con acetato de etilo, fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar [4-(metoxicarbonil)ciclohexil]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (750 mg, rendimiento 57%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,07-1,18 (2H; m); 1,33-1,49 (14H; m); 1,83-1,96 (2H; m); 2,16-2,25 (1H; m); 2,39 (3H; s); 2,48-2,56 (4H; m); 2,78 (2H; d; J = 7,4 Hz); 3,67 (3H; s); 3,78 (2H; d; J = 6,8 Hz); 4,13-4,17 (2H; m); 4,23 (1H; brs); 7,07 (2H; d; J = 7,9 Hz); 7,20 (2H; d; J = 7,7 Hz).

2) El ácido 4-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]ciclohexancarboxílico (550 mg, rendimiento 75%) fue obtenido como un sólido blanco de [4-

(metoxicarbonil)ciclohexil]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (750 mg; 1,32 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,08-1,20 (2H; m); 1,33-1,68 (14H; m); 1,86-1,96 (2H; m); 2,15-2,28 (1H; m); 2,38 (3H; s); 2,54-2,60 (4H; m); 2,78 (2H; brs); 3,78 (2H; d; J = 6,6 Hz); 4,12-4,16 (2H; m); 4,24 (1H; brs); 7,07 (2H; d; J = 7,9 Hz); 7,20 (2H; d; J = 7,7 Hz).

3) El dihidrocloruro de ácido 4-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]ciclohexancarboxílico (254 mg, rendimiento 83%) fue obtenido como un sólido blanco de ácido 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]ciclohexancarboxílico (320 mg; 0,579 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 1,17-1,42 (7H; m); 1,66-1,82 (2H; m); 2,14-2,24 (1H; m); 2,37 (3H; s); 2,41-2,45 (1H; m); 2,54 (3H; s); 2,86-2,97 (2H; m); 3,76 (2H; d; J = 6,6 Hz); 3,83 (2H; d; J = 4,7 Hz); 7,20 (2H; d; J = 7,9 Hz); 7,30 (2H; d; J = 8,1 Hz); 8,34 (3H; brs).

Ejemplo 341

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-

metilfenil)piridin-3-il]tiofen-2-carboxamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]tiofen-2-carboxamida (171mg, rendimiento 75%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de tiofen-2-carbonilo (110 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 1,00 (6H; d; J = 6,6 Hz); 2,20-2,31 (1H; m); 2,31 (3H; s); 2,63 (3H; s); 3,07 (2H; brs); 3,86 (2H; s); 7,12 (1H; dd; J = 3,3; 4,8 Hz); 7,25 (4H; s); 7,74 (1H; d; J = 3,3 Hz); 7,79 (1H; d; J = 4,8 Hz); 8,42 (3H; brs); 10,18 (1H, brs).

Ejemplo 342

Dihidrocloruro de ácido 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoico

1) El ácido 3-({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoico (110 mg, rendimiento 87%) fue obtenido como polvo blanco de metil 3-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoato (130 mg; 0,232 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ: 0,94 (6H; d; J = 6,6 Hz); 1,38 (9H; s);

2,10-2,27 (1H; m); 2,36 (3H; s); 2,89-3,10 (5H; m); 3,90 (2H; d; J = 5,7 Hz); 4,10 (2H; d; J = 7,2 Hz); 4,20 (1H; brs); 4,90 (1H; brs); 7,13 (2H; d; J = 8,1 Hz); 7,24 (2H; d; J = 8,1 Hz); 7,32 (1H; t; J = 8,0 Hz); 7,65 (1H; d J = 7,7 Hz); 7,89 (1H; s); 8,17 (1H; s).

2) El dihidrocloruro de ácido 3-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoico (95 mg, rendimiento 95%) fue obtenido como polvo blanco de ácido 3-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoico (105 mg; 0,192 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:1,00 (6H; d; J = 6,8 Hz); 2,08-2,25 (1H; m); 2,37 (3H; s); 2,51 (3H; s); 2,83 (2H; s); 3,20 (2H; s); 3,82 (2H; s); 7,09-7,51 (5H; m); 7,54-7,79 (2H; m); 8,14 (1H; s); 8,44 (3H; s); 10,34 (1H; brs).

Ejemplo 343

Dihidrocloruro de metil 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]benzoato

1) El metil 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]benzoato (350 mg, rendimiento 67%) fue obtenido como polvo blanco de ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-

metilfenil)piridin-3-il]acético (390 mg; 0,914 mmol) y metil 4-(aminometil)benzoato (553 mg; 2,74 mmol) según un método similar al método del Ejemplo 311-1).

^{1}H-RMN ($CDCl_3$) δ: 0,96 (6H; d; J = 6,6 Hz); 1,37 (9H; s); 2,11-2,29 (1H; m); 2,39 (3H; s); 2,55 (3H; s); 2,74 (2H; d; J = 7,2 Hz); 3,35 (2H; s); 3,93 (3H; s); 4,02 (2H; d; J = 5,1 Hz); 4,20 (1H; brs); 4,39 (2H; d; J = 5,8 Hz); 5,49 (1H; brs); 6,90 (2H; d; J = 7,9 Hz); 7,16 (2H; d; J = 7,9 Hz); 7,23 (2H; d; J = 8,1 Hz); 7,99 (2H; d; J = 8,1 Hz).

2) El dihidrocloruro de metil 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]benzoato (51 mg, rendimiento 89%) fue obtenido como polvo blanco de metil 4-[({[5-({[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]benzoato (60 mg; 0,105 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,11-2,27 (1H; m); 2,40 (3H; s); 2,81 (3H; s); 3,24 (2H; d; J = 6,0 Hz); 3,44 (2H; s); 3,78-3,89 (5H; m); 4,28 (2H; d; J = 5,5 Hz); 7,20 (2H; d; J = 7,9 Hz); 7,27-7,38 (5H; m);7,94 (2H; d; J = 7.9 Hz); 8.54 (3H; brs).

Ejemplo 344

Dihidrocloruro de ácido 5-[({[5-(aminometil)-6-isobutil-2-

metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]pirazin-2-carboxílico

1) El metil 5-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]pirazin-2-carboxilato (1,35 g; rendimiento 98%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,00 g; 2,43 mmol) y metil 5-(bromometil)pirazin-2-carboxilato (0,51 g; 2,21 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s), 2,17-2,27 (1H; m); 2,31 (3H; s); 2,58 (3H; s); 2,79 (2H; d; J = 7,2 Hz); 4,06 (3H; s); 4,12-4,16 (2H; m); 4,22 (1H; brs); 5,13 (2H; s); 7,02 (2H; d; J = 8,1 Hz); 7,10 (2H; d; J = 7,9 Hz); 8,36 (1H; d; J = 1,3 Hz); 9,19 (1H; d; J = 1,3 Hz).

2) El ácido 5-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]pirazin-2-carboxílico (600 mg, rendimiento 45%) fue obtenido como un aceite incoloro de metil 5-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]pirazin-2-carboxilato (1,35 g; 2,40 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,16-

2,28 (1H; m); 2,33 (3H; s); 2,59 (3H; s); 2,82 (2H; d; J = 7,4 Hz); 4,11-4,19 (2H; m); 4,24 (1H; brs); 5,18 (2H; s); 7,04 (2H; d; J = 7,9 Hz); 7,12 (2H; d; J = 7,2 Hz); 8,20 (1H; s); 9,30 (1H; s).

3) El dihidrocloruro de ácido 5-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]pirazin-2-carboxílico (497 mg, rendimiento 76%) fue obtenido como un sólido amarillo del ácido 5-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]pirazin-2-carboxílico (600 mg; 1,09 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,17-2,26 (1H; m); 2,29 (3H; s); 2,62 (3H; brs); 2,94 (2H; brs); 3,80 (2H; d; J = 4,7 Hz); 5,23 (2H; s); 7,08-7,18 (4H; m); 8,38 (3H; brs); 8,43 (1H; d; J = 1,3 Hz); 9,10 (1H; d; J = 1,3 Hz).

Ejemplo 345

Dihidrocloruro de 4-bromobencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

Dihidrocloruro de 4-bromobencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (628 mg, rendimiento 90%) fue obtenido como un sólido blanco de 4-bromobencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (0,73 g; 1,26 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,8 Hz); 2,14-2,27 (1H; m); 2,36 (3H; s); 2,87 (2H; brs); 3,80 (2H; d; J = 5,3 Hz); 4,97 (2H; s); 7,00 (2H; d; J = 8,5 Hz); 7,12 (2H; d; J = 8,1 Hz); 7,19 (2H; d; J = 8,1 Hz); 7,50 (2H; d; J = 8,5 Hz); 8,26 (3H, brs).

Ejemplo 346

Dihidrocloruro de {[5-[(2-bromofenoxi)metil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}amina

1) Terc-butil {[5-[(2-bromofenoxi)metil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (640 mg, rendimiento 46%) fue obtenido como un sólido blanco del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,00 g; 2,51 mmol) y 2-bromofenol (478 mg, 2,76 mmol) según un método similar al método del Ejemplo 214-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,19-2,28 (1H; m); 2,37 (3H; s); 2,69 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 4,08-4,11 (2H; m); 4,24 (1H; brs); 4,67 (2H; s); 6,65 (1H; dd; J = 8,1; 1,3 Hz); 6,79-6,84 (1H; m); 7,07 (2H; d; J = 8,1 Hz); 7,12-7,19 (3H; m); 7,51 (1H; dd; J = 7,9; 1,5 Hz).

2) El dihidrocloruro de {[5-[(2-Bromofenoxi)metil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}amina (458 mg, rendimiento 75%) fue obtenido como un sólido blanco

del terc-butil {[5-[(2-bromofenoxi)metil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (640 mg; 1,16 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,01 (6H; d; J = 6,6 Hz); 2,16-2,30 (1H; m); 2,36 (3H; s); 2,91 (3H; brs); 3,20 (2H; brs); 3,79-3,90 (2H; m); 4,79 (2H; s); 6,89-6,95 (2H; m); 7,25-7,36 (5H; m); 7,58 (1H; dd; J = 7,7; 1,5 Hz); 8,48 (3H; brs).

Ejemplo 347

Dihidrocloruro de ácido 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-metoxibenzoico

1) El 2-Metoxi-4-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,15 g; rendimiento 100%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (0,80 g; 1,94 mmol) y metil 4-(bromometil)-3-metoxibenzoato (503 mg, 1.94 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,15-2,24 (1H; m); 2,34 (3H; s); 2,54 (3H; s); 2,77 (2H; d; J = 7,2 Hz); 3,85 (3H; s); 3,93 (3H; s); 4,10-4,16 (2H; m); 4,20 (1H; brs); 5,06 (2H; s); 6,96 (1H; d; J = 7,9 Hz); 7,03 (2H; d, J = 8,1 Hz); 7,10 (2H; d; J = 7,9 Hz); 7,48-7,53 (2H; m).

2) El ácido 4-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-metoxibenzoico (1,10 g; rendimiento 97%) fue obtenido como un aceite incoloro de 2-metoxi-4-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,15 g; 1,94 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,16-2,26 (1H; m); 2,35 (3H; s); 2,56 (3H; s); 2,80 (2H; d; J = 7,2 Hz); 3,86 (3H; s); 4,11-4,16 (2H; m); 4,23 (1H; brs); 5,08 (2H; s); 6,97 (1H; d; J = 7,9 Hz); 7,04 (2H; d; J = 7,7 Hz); 7,11 (2H; d; J = 7,7 Hz); 7,53 (1H; s); 7,58 (1H; d; J = 7,9 Hz).

3) El dihidrocloruro de ácido 4-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-metoxibenzoico (247 mg; rendimiento 74%) fue obtenido como un sólido blanco de ácido 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-metoxibenzoico (0,35 g; 0,607 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,17-2,26 (1H; m); 2,32 (3H; s); 2,84 (2H;brs); 3,79 (2H; d; J = 5,7 Hz); 3,83 (3H; s); 5,03 (2H; s); 6,96 (1H; d; J = 7,7 Hz); 7,13

(2H; d; J = 8,1 Hz); 7,18 (2H; d; J = 8,1 Hz); 7,42-7,45 (1H; m); 7,46 (1H; s); 8,19 (3H; brs).

Ejemplo 348

Dihidrocloruro de ácido 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-2-metoxibenzoico

1) 3-Metoxi-4-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (680 mg, rendimiento 94%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (0,50 g; 1,22 mmol) y metil 4-(bromometil)-2-metoxibenzoato (315 mg; 1,22 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,16-2,25 (1H; m); 2,33 (3H; s); 2,54 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 3,86 (3H; s); 3,90 (3H; s); 4,11-4,13 (2H; m); 4,21 (1H; brs); 4,94 (2H; s); 6,65 (1H; dd; J = 8,0; 1,4 Hz); 6,75 (1H; d; J = 1,1 Hz); 6,99 (2H; d; J = 8,1 Hz); 7,08 (2H; d; J = 7,7 Hz); 7,70 (1H; d; J = 7,9 Hz).

2) El ácido 4-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-2-metoxibenzoico (550 mg, rendimiento 83%) fue obtenido como un aceite incoloro de 3-metoxi-4-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-

6-isobutil-2-metil-4-(4-metilfenil)nicotinato (680 mg; 1,15 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,16-2,25 (1H; m); 2,33 (3H; s); 2,54 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 4,04 (3H; s); 4,11-4,13 (2H; m); 4,20 (1H; brs); 4,98 (2H; s); 6,77 (1H; d; J = 9,4 Hz); 6,84 (1H; s); 6,99 (2H; d; J = 8,1 Hz); 7,07 (2H; d; J = 7,9 Hz); 8,08 (1H; d; J = 7,9 Hz).

3) El dihidrocloruro de ácido 4-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-2-metoxibenzoico (240 mg, rendimiento 85%) fue obtenido como un sólido blanco de ácido 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-2-metoxibenzoico (293 mg; 0,509 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,14-2,26 (1H; m); 2,33 (3H; s); 2,58 (3H; brs); 2,93 (2H; brs); 3,78 (3H; s); 3,81 (2H; d; J = 4,5 Hz); 5,01 (2H; s); 6,62 (1H; d; J = 7,9 Hz); 6,92 (1H; d; J = 0,9 Hz); 7,12-7,22 (4H; m); 7,55 (1H; d; J = 7,7 Hz); 8,37 (3H; brs).

Ejemplo 349

Dihidrocloruro de ácido 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-

il]acetil}amino)metil]benzoico

1) El ácido 4-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]benzoico (182 mg, rendimiento 94%) fue obtenido como polvo blanco de metil 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]benzoato (200 mg; 0,349 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ: 0,92 (6H; d; J = 6,6 Hz); 1,34 (9H; s); 2,10-2,24 (1H; m); 2,35 (3H; s); 2,38 (3H; s); 2,58 (2H; s); 3,22 (2H; s); 3,77 (2H; d; J = 3,0 Hz); 4,20 (1H; brs); 4,27 (2H; d; J = 5,8 Hz); 6,74 (1H; s); 7,09 (2H; d; J = 8,1 Hz); 7,17 (2H; d; J = 8,1 Hz); 7,28 (2H; d; J = 8,3 Hz); 7,90 (2H; d; J = 8,3 Hz); 8,17 (1H; s).

2) El dihidrocloruro de ácido 4-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]benzoico (135 mg, rendimiento 95%) fue obtenido como polvo blanco de ácido 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]benzoico (150 mg; 0,268 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,98 (6H; d; J = 6,6 Hz); 2,07-2,24 (1H; m);

2,40 (3H; s); 2,78 (3H; s); 3,10 (2H; s); 3,41 (2H; s); 3,78 (2H; s); 4,27 (2H; d; J = 5,7 Hz); 7,16 (2H; d; J = 7,9 Hz); 7,26-7,34 (4H; m);7,92 (2H; d; J = 8,3 Hz); 8,33 (3H; brs); 8.45 (1H; brs).

Ejemplo 350

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]isoxazol-4-carboxamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]isoxazol-4-carboxamida (173 mg, rendimiento 76%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de isoxazol-4-carbonilo (100 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 0,99 (6H; d; J = 6,6 Hz); 2,20-2,31 (1H; m); 2,53 (3H; s); 2,94 (2H; s); 3,82 (2H; brs); 7,09 (1H; s); 7,20 (2H; d; J = 8,1 Hz); 7,25 (2H; d; J = 8,1 Hz); 8,28 (3H; brs); 8,73 (1H; brs); 10,59 (1H; brs).

Ejemplo 351

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]furan-2-carboxamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]furan-2-carboxamida (190 mg, rendimiento 85%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-

il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de furan-2-carbonilo (100 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 1,00 (6H; d; J = 6,6 Hz); 2,09-2,30 (1H; m); 2,32 (3H; s); 2,58 (3H; s); 3,04 (2H; brs); 3,83 (2H; s); 6,61 (1H; dd; J = 1,8; 3,3 Hz); 7,14 (1H; d; J = 3,3 Hz); 7,21 (2H; d; J = 7,8 Hz); 7,25 (2H; d; J = 7,8 Hz); 7,84 (1H; s); 8,37 (3H; brs); 9,98 (1H; brs).

Ejemplo 352

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-metilbenzamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-metilbenzamida (211 mg, rendimiento 87%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de 4-metilbenzoilo (116 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 1,00 (6H; d; J = 6,6 Hz); 2,22-2,32 (1H; m); 2,31 (3H; s); 2,32 (3H; s); 2,57 (3H; s); 3,01 (2H; brs); 3,84 (2H; s); 7,21-7,27 (6H; m); 7,55 (2H; d; J = 8,1 Hz); 8,32 (3H; brs); 9,88 (1H; brs).

Ejemplo 353

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-

metilfenil)piridin-3-il]-4-terc-butilbenzamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-terc-butilbenzamida (211 mg, rendimiento 83%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de 4-terc-butilbenzoilo (147 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 1,00 (6H; d; J = 6,6 Hz); 1,27 (9H; s); 2,22-2,31 (1H; m); 2,31 (3H; s); 2,56 (3H; s); 3,01 (2H; brs); 3,84 (2H; s); 7,21-7,26 (4H; m); 7,44 (2H; d; J = 8,4 Hz); 7,60 (2H; d; J = 8,4 Hz); 8,32 (3H; brs); 9,91 (1H; brs).

Ejemplo 354

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-clorobenzamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-clorobenzamida (203 mg, rendimiento 82%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de 4-clorobenzoilo (131 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 1,00 (6H; d; J = 6,6 Hz); 2,20-2,30 (1H;

m); 2,31 (3H; s); 2,62 (3H; s); 3,08 (2H; brs); 3,86 (2H; s); 7,25 (4H; s); 7,52 (2H; d; J = 8,4 Hz); 7,67 (2H; d; J = 8,4 Hz); 8,41 (3H; brs); 10,20 (1H; brs).

Ejemplo 355

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-cianobenzamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-cianobenzamida (209mg, rendimiento 86%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de 4-cianobenzoilo (126mg; 0c75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 1,00 (6H; d; J = 6,6 Hz); 2,10-2,31(1H; m); 2,31 (3H; s); 2,59 (3H; s); 3,02 (2H; brs); 3,85 (2H; s); 7,24 (4H; s); 7,76 (2H; d; J = 8,1 Hz); 7,94 (2H; d; J = 8,1 Hz); 8,36(3H; brs); 10,36 (1H; brs).

Ejemplo 356

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-trifluorometilbenzamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-trifluorometilbenzamida (209 mg, rendimiento 86%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y

cloruro de 4-trifluorometilbenzoilo (156 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 1,00 (6H; d; J = 6,6 Hz); 2,21-2,32 (1H; m); 2,31 (3H; s); 2,55 (3H; s); 2,96 (2H; brs); 3,83 (2H; s); 7,22 (2H; d; J = 7,8 Hz); 7,26 (2H; d; J = 7,8 Hz); 7,78 (2H; d; J = 7,8 Hz); 7,82 (2H; d; J = 7,8 Hz); 8,27 (3H; brs); 10,21 (1H; brs).

Ejemplo 357

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]furan-3-carboxamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]furan-3-carboxamida (190 mg, rendimiento 85%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de furan-3-carbonilo (100 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 0,99 (6H; d; J = 6,6 Hz); 2,21-2,32 (1H; m); 2,55 (3H; s); 2,98 (3H; s); 3,82 (2H; brs); 6,74 (1H; s); 7,20 (2H; d; J = 7,8 Hz); 7,25 (2H; d; J = 7,8 Hz); 7,69 (1H; s); 8,15 (1H; s); 8,30 (3H; brs); 9,74 (1H; brs).

Ejemplo 358

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]tiofen-3-carboxamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]tiofen-3-carboxamida (233 mg, rendimiento 99%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de tiofen-3-carbonilo (110 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 0,99 (6H; d; J = 6,6 Hz); 2,20-2,31 (1H; m); 2,31 (3H; s); 2,59 (3H; s); 3,05 (2H; brs); 3,84 (2H; s); 7,24 (4H; s); 7,36 (1H; dd; J = 1,2; 5,1 Hz); 7,56 (1H; dd; J = 5,1; 2,7 Hz); 8,10 (1H; d; J = 2,7 Hz); 8,35 (3H; brs); 9,91 (1H; brs).

Ejemplo 359

Dihidrocloruro de ácido 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-fluorobenzoico

1) 2-Fluoro-4-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (650 mg, rendimiento 92%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (0,50 g; 1,21 mmol) y metil 4-(bromometil)-3-fluorobenzoato (299 mg; 1,21 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,8 Hz); 1,38 (9H; s); 2,16-

2,25 (1H; m); 2,33 (3H; s); 2,54 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,94 (3H; s); 4,09-4,13 (2H; m); 4,20 (1H; brs); 5,05 (2H; s); 6,98-7,09 (5H; m); 7,64-7,71 (2H; m).

2) El ácido 4-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-fluorobenzoico (450 mg, rendimiento 71%) fue obtenido como un aceite incoloro de 2-fluoro-4-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (650 mg; 1,12 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,38 (9H; s); 2,13-2,25 (1H; m); 2,33 (3H; s); 2,56 (3H; s); 2,80 (2H; d; J = 7,2 Hz); 4,09-4,16 (2H; m); 4,22 (1H; brs); 5,07 (2H; s); 7,00-7,12 (5H; m); 7,70-7,76 (2H; m).

3) El dihidrocloruro de ácido 4-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-fluorobenzoico (329 mg, rendimiento 76%) fue obtenido como un sólido blanco de ácido 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-fluorobenzoico (450 mg; 0,797 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,95 (6H; d; J = 6,6 Hz); 2,16-2,23 (1H; m); 2,29 (3H; s); 2,86 (2H; brs); 3,78 (2H; d; J = 5,5 Hz);

5,11 (2H; s); 7,07-7,13 (4H; m); 7,18 (1H; t; J = 7,6 Hz); 7,60-7,69 (2H; m); 8,23 (3H; brs).

Ejemplo 360

Dihidrocloruro de ácido 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-clorobenzoico

1) 2-cloro-4-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (518 mg, rendimiento 99%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (0,36 g; 0,873 mmol) y 4-(bromometil)-3-clorobenzoato de metilo (230 mg; 0,873 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,38 (9H; s); 2,17-2,26 (1H; m); 2,32 (3H; s); 2,56 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 3,94 (3H; s); 4,11-4,13 (2H; m); 4,22 (1H; brs); 5,11 (2H; s); 7,02-7,04 (3H; m); 7,09 (2H; d; J = 8,1 Hz); 7,78 (1H; dd; J = 8,0; 1,6 Hz); 7,99 (1H; d; J = 1,5 Hz).

2) El ácido 4-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-clorobenzoico (420 mg, rendimiento 83%) fue obtenido como un sólido blanco de 2-cloro-4-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (518 mg; 0,870

mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,22-2,33 (4H; m); 2,59 (3H; brs); 2,82 (2H; brs); 4,09-4,17 (2H; m); 4,25 (1H; brs); 5,13 (2H; s); 7,01-7,14 (5H; m); 7,83 (1H; dd; J = 8,0; 1,6 Hz); 8,04 (1H; d; J = 1,5 Hz).

3) El dihidrocloruro de ácido 4-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-clorobenzoico (265 mg, rendimiento 66%) fue obtenido como un sólido blanco de ácido 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-clorobenzoico (420 mg; 0,722 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,15-2,24 (1H; m); 2,29 (3H; s); 2,54 (3H; s); 2,86 (2H; brs); 3,79 (2H; d; J = 5,3 Hz); 5,14 (2H; s); 7,13 (4H; s); 7,16 (1H; d; J = 7,9 Hz); 7,78 (1H; dd; J = 7,9; 1,5 Hz); 7,90 (1H; d; J = 1,5 Hz), 8.25 (3H, brs).

Ejemplo 361

Dihidrocloruro de ácido 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]isoftálico

1) El dimetil 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-

il]carbonil}oxi)metil]isoftalato (1,12 g; rendimiento 99%) fue obtenido como un aceite incoloro de ácido 5-({[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (0,75 g; 1,82 mmol) y dimetilo 4-(bromometil)isoftalato (522 mg; 1,82 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,15-2,26 (1H; m); 2,35 (3H; s); 2,57 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 3,91 (3H; s); 3,96 (3H; s); 4,11-4,16 (2H; m); 4,23 (1H; brs); 5,45 (2H; s); 6,99 (1H; d; J = 8,1 Hz); 7,06 (2H; d; J = 8,3 Hz); 7,13 (2H; d; J = 7,9 Hz); 7,99 (1H; dd; J = 8,1; 1,9 Hz); 8,59 (1H; d; J = 1,9 Hz).

2) El ácido 4-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]isoftálico (750 mg, rendimiento 68%) fue obtenido como un aceite incoloro del dimetil 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]isoftalato (1,12 g; 1,81 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,4 Hz); 1,38 (9H; s); 2,23-2,35 (4H; m); 2,58 (3H; s); 2,86 (2H; d; J = 5,1 Hz); 4,11-4,21 (2H; m); 4,35 (1H; brs); 5,48 (2H; s); 7,01-7,17 (5H; m); 7,96-8,08 (1H; m); 8,64-8,75 (1H; m).

3) El dihidrocloruro de ácido 4-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]isoftálico (362 mg, rendimiento 90%) fue obtenido como un sólido blanco de ácido 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]isoftálico (420 mg; 0,711 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,16-2,27 (1H; m); 2,33 (3H; s); 2,57 (3H; brs); 2,90 (2H; brs); 3,82 (2H; d; J = 5,1 Hz); 5,42 (2H; s); 7,01 (1H; d; J = 8,1 Hz); 7,19 (2H; d; J = 8,7 Hz); 7,23 (2H; d; J = 8,3 Hz); 7,97 (1H; dd; J = 8,1; 1,9 Hz); 8,31 (3H; brs); 8,42 (1H; d; J = 1,9 Hz).

Ejemplo 362

Trihidrocloruro de 2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-N-[4-(dimetilamino)fenil]acetamida

1) Terc-butil {[5-(2-{[4-(dimetilamino)fenil]amino}-2-oxoetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (450 mg, rendimiento 71%) fue obtenido como polvo blanco de ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acético (500 mg; 1,17 mmol) y 4-(dimetilamino)anilina (500 mg; 3,67 mmol) según un método similar al método del Ejemplo 311-1).

^{1}H-RMN ($CDCl_3$) δ: 0,98 (6H; d; J = 6,6 Hz); 1,38 (9H; s);

2,16-2,27 (1H; m); 2,40 (3H; s); 2,63 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 2,90 (6H; s); 3,42 (2H; s); 4,06 (2H; d; J = 5,1 Hz); 4,20 (1H; brs); 6,58 (1H; brs); 6,66 (2H; d; J = 8,1 Hz); 7,02 (2H; d; J = 7,7 Hz); 7,18 (2H; d; J = 8,1 Hz); 7,24 (2H; d; J = 7,7 Hz).

2) El trihidrocloruro de 2-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-N-[4-(dimetilamino)fenil]acetamida (62 mg, rendimiento 42%) fue obtenido como polvo de color de violeta del terc-butil ([5-(2-{[4-(dimetilamino)fenil]amino}-2-oxoetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil)carbamato (100 mg; 0,268 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,4 Hz); 2,13-2,28 (1H; m); 2,38 (3H; s); 2,76 (3H; s); 3,01 (6H; s); 3,13 (2H; s); 3,77-3,86 (5H; m); 7,20 (2H; d; J = 8,1 Hz); 7,35 (2H; d; J = 8,1 Hz); 7,51 (2H; d; J = 8,1 Hz); 8,30 (2H; d; J = 8,1 Hz) 8,56 (3H, brs).

Ejemplo 363

Etil 5-(aminometil)-4-(4-metilfenil)-2,6-dineopentilnicotinato

1) Una mezcla de 3-etoxi-3-oxopropionato de potasio (7,6 g; 45 mmol), cloruro de magnesio (2,8 g; 30 mmol) y tetrahidrofurano (75 mL) fue agitada a 50°C por 4 hrs. A la suspensión obtenida se le permitió enfriar a la temperatura

ambiente, y una mezcla de reacción se obtuvo agitando una mezcla de ácido terc-butilacético (3,5 g; 30 mmol), N,N'-carbonildiimidazol (5,8 g; 36 mmol) y fue agregado por gotas tetrahidrofurano (50 mL) a la temperatura ambiente durante 1 hr a la suspensión. La mezcla resultante fue agitado a temperatura ambiente durante 3 días. La mezcla de reacción fue dividida entre acetato de etilo y 0,5N de ácido clorhídrico. La capa orgánica fue lavada consecutivamente con carbonato hidrógeno de sodio acuoso saturado y solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida para dar etil 5,5-dimetil-3-oxohexanoato como un producto en bruto (5,9 g). Una mezcla del producto en bruto (5,9 g), acetato de amonio (9,8 g; 127 mmol), ácido acético (1,45 mL; 25 mmol) y tolueno (200 mL) fue calentada bajo reflujo usando una trampa Dean-Stark por 17 hrs. A la mezcla de reacción se le permitió enfriar a la temperatura ambiente, fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar el etil 3-amino-5,5-dimetilhex-2-enoato (2,5 g; rendimiento 52%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$)δ: 1,00 (9H; s); 1,27 (3H; t; J = 7,2 Hz); 1,98 (2H; s); 4,11 (2H; q; J = 7,2 Hz); 4,45 (2H; brs); 8,05 (1H;

s).

2) El etil 5-ciano-4-(4-metilfenil)-2;6-dineopentil-1;4-dihidropiridin-3-carboxilato (3,5 g; rendimiento 65%) fue obtenido como polvo blanco de 5,5-dimetil-3-oxohexannitrilo (2,4 g; 13 mmol), p-tolualdehído (1,6 g; 13 mol) y etil 3-amino-5,5-dimetilhex-2-enoato (2,5 g; 13 mmol) según un método similar al método del Ejemplo 1-2).

^{1}H-RMN ($CDCl_3$)δ: 1,01 (9H; s); 1,03 (9H; s); 1,17 (3H; t; J = 7,2 Hz); 2,06 (1H; d; J = 13,7 Hz); 2,27 (1H; d; J = 13,7 Hz); 2,31 (3H; s); 2,52 (1H; d; J = 13,7 Hz); 3,34 (1H; d; J = 13,7 Hz); 3,95-4,10 (2H; m); 4,63 (1H; s); 5,44 (1H; brs); 7,09 (2H; d; J = 8,0 Hz); 7,17 (2H; d; J = 8,0 Hz).

3) El etil 5-ciano-4-(4-metilfenil)-2,6-dineopentilnicotinato (3,2 g; rendimiento 96%) fue obtenido como polvo blanco de etil 5-ciano-4-(4-metilfenil)-2,6-dineopentil-1,4-dihidropiridin-3-carboxilato (3,4 g; 8,2 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$)δ: 0,91 (3H; t; J = 7,2 Hz); 1,01 (9H; s); 1,08 (9H; s); 2,40 (3H; s); 2,87 (2H; s); 3,02 (2H; s); 3,99 (2H; q; J = 7,2 Hz); 7,20-7,30 (4H; m),

4) El etil 5-(aminometil)-4-(4-metilfenil)-2,6-dineopentilnicotinato (0,91 g; rendimiento 90%) fue obtenido como un aceite incoloro de etil 5-ciano-4-(4-metilfenil)-2,6-dineopentilnicotinato (1,0 g; 2,5 mmol) según un método

similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$)δ: 0,89 (3H; t; J = 7,2 Hz); 0,99 (9H; s); 1,04 (9H; s); 1,33 (2H; brs); 2,38 (3H; s); 2,78 (2H; s); 2,88 (2H; s); 3,72 (2H; s); 3,89 (2H; q; J = 7,2 Hz); 7,12 (2H; d; J = 8,0 Hz); 7,20, (2H; d; J = 8,0 Hz).

Ejemplo 364

Dihidrocloruro de 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}propan-1-ol

1) Una mezcla de metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metilo (1,91 g; 4,01 mmol); 1,3-propandiol (3,05 g; 40,1 mmol), hidruro de sodio (60% en aceite, 1,60 g; 40,1 mmol) y tetrahidrofurano (5 mL) fue agitado a 55°C por 16 hrs. A la mezcla de reacción se le permitió enfriar a la temperatura ambiente y fue agregado 1N de ácido clorhídrico para detener la reacción. La mezcla de reacción fue diluída con acetato de etilo y lavada con solución salina saturada. La capa orgánica fue secada sobre sulfato de magnesio y el solvente fue evaporado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice para dar terc-butil {[5-[(3-hidroxipropoxi)metil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (840 mg, rendimiento 46%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s);

1,70-1,80 (2H; m); 2,16-2,27 (1H; m); 2,42 (3H; s); 2,63 (3H; s); 2,75 (2H; d; J = 7,4 Hz); 3,40 (2H; t; J = 5,8 Hz); 3,70 (2H; t; J = 5,8 Hz); 4,06 (2H; d; J = 4,7 Hz); 4,10 (2H; s); 4,20 (1H; brs); 7,03 (2H; d; J = 7,9 Hz); 7,24 (2H; d; J = 7,9 Hz).

2) El dihidrocloruro de 3-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}propan-1-ol (15 mg, rendimiento 100%) fue obtenido como polvo blanco del terc-butil {[5-[(3-hidroxipropoxi)metil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (18 mg; 0,0394 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,4 Hz); 1,70-2,3 (2H; m);2,38 (3H; s); 2,75 (2H; s); 3,35-4,20 (6H; m); 4,06 (2H; d; J = 4,5 Hz); 4,11 (2H; d; J = 4,5 Hz); 7,00 (2H; d; J = 8,1 Hz); 7,30 (2H; d; J = 8,1 Hz); 7,51 (2H; d; J = 8,1 Hz); 8,56 (3H; brs).

Ejemplo 365

Dihidrocloruro de ácido 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]ftálico

1) El dimetil 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]ftalato (1,68 g; rendimiento 95%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,18 g; 2,86 mmol) y dimetil 4-

(bromometil)ftalato (820 mg, 2,86 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,17-2,26 (1H; m); 2,33 (3H; s); 2,54 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 3,92 (3H; s); 3,93 (3H; s); 4,11-4,15 (2H; m); 4,21 (1H; brs); 4,95 (2H; s); 7,00 (2H; d; J = 8,1 Hz); 7,09 (2H; d; J = 7,9 Hz); 7,16 (1H; dd; J = 7,9; 1,7 Hz); 7,47 (1H; d; J = 1,5 Hz); 7,62 (1H; d; J = 7,7 Hz).

2) El ácido 4-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]ftálico (1,60 g; rendimiento 99%) fue obtenido como un aceite incoloro del dimetil 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]ftalato (1,68 g; 2,72 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:1,00 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,16-2,27 (1H; m); 2,39 (3H; s); 2,67 (3H; brs); 3,10 (2H; d; J = 7,0 Hz); 4,23 (2H; d; J = 4,9 Hz); 4,51 (1H; brs); 5,01 (2H; s); 7,07 (2H; s); 7,21-7,24 (3H; m); 8,03 (1H; s); 8,13 (1H; d; J = 7,9 Hz).

3) El dihidrocloruro de ácido 4-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]ftálico (396 mg; rendimiento 84%) fue

obtenido como un sólido blanco de ácido 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]ftálico (0,49 g; 0,830 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,6 Hz); 2,17-2,26 (1H; m); 2,33 (3H; s); 2,56 (3H; brs); 2,91 (2H; brs); 3,81 (2H; d; J = 4,9 Hz); 5,05 (2H; s); 7,13 (2H; d; J = 7,9 Hz); 7,17-7,21 (3H; m); 7,39 (1H; d; J = 1,5 Hz); 7,59 (1H; d; J = 7,9 Hz); 8,32 (3H; brs).

Ejemplo 366

Dihidrocloruro de ácido 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-2-fluorobenzoico

1) 4-Bromo-3-fluorobencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,36 g; rendimiento 78%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,20 g; 2,91 mmol) y (4-bromo-3-fluorofenil)metanol (597 mg; 2,91 mmol) según un método similar al método del Ejemplo 247-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,16-2,25 (1H; m); 2,36 (3H; s); 2,55 (3H; s); 2,78 (2H; d; J =

7,2 Hz); 4,11-4,16 (2H; m); 4,21 (1H; brs); 4,86 (2H; s); 6,61-6,65 (1H; m); 7,00-7,06 (3H; m); 7,12-7,19 (3H; m).

2) El 3-Fluoro-4-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (520 mg, rendimiento 39%) fue obtenido como un aceite amarillo de 4-bromo-3-fluorobencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1,36 g; 2,27 mmol) según un método similar al método del Ejemplo 231-2).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,15-2,25 (1H; m); 2,33 (3H; s); 2,55 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 3,94 (3H; s); 4,09-4,15 (2H; m); 4,21 (1H; brs); 4,94 (2H; s); 6,81-6,85 (1H; m); 7,00 (2H; d; J = 8,1 Hz); 7,10 (2H; d; J = 7,9 Hz); 7,63-7,67 (2H; m).

3) El ácido 4-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-2-fluorobenzoico (480 mg, rendimiento 94%) fue obtenido como un aceite incoloro de 3-fluoro-4-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (520 mg; 0,899 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,16-2,26 (1H; m); 2,33 (3H; s); 2,56 (3H; s); 2,81 (2H; d; J = 7,4 Hz); 4,09-4,16 (2H; m); 4,24 (1H; brs); 4,96 (2H; s);

6,88-6,92 (1H; m); 7,02 (2H; d; J = 7,9 Hz); 7,11 (2H; d; J = 7,9 Hz); 7,69-7,73 (2H; m).

4) El dihidrocloruro de ácido 4-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-2-fluorobenzoico (192 mg, rendimiento 42%) fue obtenido como un sólido blanco de ácido 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-2-fluorobenzoico (480 mg; 0,850 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,96 (6H; d; J = 6,8 Hz); 2,12-2,26 (1H; m); 2,30 (3H; s); 2,53 (3H; s); 2,86 (2H; d; J = 7,0 Hz); 3,79 (2H; d; J = 5,7 Hz); 5,05 (2H; s); 7,05-7,16 (5H; m); 7,59-7,64 (2H; m); 8,24 (3H; brs).

Ejemplo 367

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-oxo-4,5,6,7-tetrahidro-1-benzofuran-3-carboxamida

Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-oxo-4,5,6,7-tetrahidro-1-benzofuran-3-carboxamida (172 mg, rendimiento 66%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de 4-oxo-4,5,6,7-tetrahidro-1-benzofuran-3-carbonilo (150 mg; 0,75 mmol) según un método

similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 1,10 (6H; el d; J = 6,6 Hz); 2,00-2,09 (2H; m); 2,11-2,31 (1H; m); 2,31 (3H; s); 2,44 (2H; t; J = 6,3 Hz); 2,59 (3H; s); 2,93 (2H; t; J = 6,3 Hz); 3,06 (2H; s); 3,85 (2H; s); 7,24 (4H; s); 8,35 (1H; s); 8,36 (3H; brs); 11,42 (1H; brs).

Ejemplo 368

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2-fenil-1,3-tiazol-4-carboxamida

Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2-fenil-1,3-tiazol-4-carboxamida (155 mg, rendimiento 57%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de 2-fenil-1,3-tiazol-4-carbonilo (167 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 1,00 (6H; el d; J = 6,6 Hz); 2,20-2,29 (1H; m); 2,28 (3H; s); 2,61 (3H; s); 3,04 (2H; s); 3,85 (2H; s); 7,26 (4H; s); 7,53-7,55 (3H; m); 7,95-7,98 (2H; m); 8,35 (1H; s); 8,36 (3H; brs); 9,85 (1H; brs).

Ejemplo 369

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]pirazin-2-carboxamida

Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-

4-(4-metilfenil)piridin-3-il]pirazin-2-carboxamida (157 mg, rendimiento 63%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de pirazin-2-carbonilo (107 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 1,01 (6H; d; J = 6,6 Hz); 2,18-2,28 (1H; m); 2,27 (3H; s); 2,63 (3H; s); 3,12 (2H; s); 3,85 (2H; s); 7,21 (2H; d; J = 8,1 Hz); 7,26 (2H; d; J = 8,1 Hz); 8,46 (3H; brs); 8,70 (1H; s); 8,88 (1H; s); 9,08 (1H; s); 10,48 (1H; brs).

Ejemplo 370

Dihidrocloruro de ácido 4-[({[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetil}oxi)metil]benzoico

1) 6N ácido clorhídrico (200 mL) fue agregado al terc-butil {[5-(cianometil)-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (16 g; 37 mmol) y la mezcla fue agitada a 90°C por 24 hrs. La mezcla de reacción fue lavada con una mezcla de solvente de tetrahidrofurano-tolueno (1:2) y fue concentrada bajo presión reducida. El residuo fue disuelto en agua y alcalinizado agregando solución 4N de hidróxido de sodio acuosa. La solución alcalificada obtenida fue lavada con acetato de etilo y fue concentrada bajo presión reducida. Fue agregado tetrahidrofurano (100 mL) y agua (50 mL) al residuo y la mezcla fue agitada vigorosamente. El

similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 1,10 (6H; el d; J = 6,6 Hz); 2,00-2,09 (2H; m); 2,11-2,31 (1H; m); 2,31 (3H; s); 2,44 (2H; t; J = 6,3 Hz); 2,59 (3H; s); 2,93 (2H; t; J = 6,3 Hz); 3,06 (2H; s); 3,85 (2H; s); 7,24 (4H; s); 8,35 (1H; s); 8,36 (3H; brs); 11,42 (1H; brs).

Ejemplo 368

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2-fenil-1,3-tiazol-4-carboxamida

Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2-fenil-1,3-tiazol-4-carboxamida (155 mg, rendimiento 57%) fue obtenido como polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y cloruro de 2-fenil-1,3-tiazol-4-carbonilo (167 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ: 1,00 (6H; el d; J = 6,6 Hz); 2,20-2,29 (1H; m); 2,28 (3H; s); 2,61 (3H; s); 3,04 (2H; s); 3,85 (2H; s); 7,26 (4H; s); 7,53-7,55 (3H; m); 7,95-7,98 (2H; m); 8,35 (1H; s); 8,36 (3H; brs); 9,85 (1H; brs).

Ejemplo 369

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]pirazin-2-carboxamida

Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-

dicarbonate de di-terc-butilo (8,5 mL; 37 mmol) fue agregado por gotas y la mezcla fue agitada a la temperatura ambiente por 17 hrs. Fue agregado 1N de ácido clorhidrico a la mezcla de reacción para acidificar la capa acuosa y la mezcla fue extractada con acetato de etilo. Los extractos fueron combinados, fueron lavados con solución salina saturada y fueron secados sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue cristalizado desde hexano - acetato de etilo para dar ácido [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acético (13 g; rendimiento 80%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$)δ: 1,09 (9H; s); 1,39 (9H; s); 2,43 (3H; s); 2,82 (3H; d; J = 20 Hz); 3,34 (2H; brs); 3,43 (2H; brs); 4,05-4,25 (2H; m); 4,35-4,50 (1H; m); 6,97 (2H; dd; J = 7,5; 24 Hz); 7,26 (2H; dd; J = 7,5; 29 Hz).

2) Una mezcla de ácido [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acético (0,50 g; 1,1 mmol), trietilamina (0,17 mL; 1,3 mmol) y tetrahidrofurano (20 mL) fue enfriado con hielo y una solución de cloruro de 2,4,6-triclorobenzoilo (0,31 g; 1,3 mmol) en tetrahidrofurano (2 mL) fue agregado por gotas. La mezcla obtenida fue agitado a temperatura ambiente por 14 hrs. La mezcla de reacción fue filtrada y el filtrado fue concentrado bajo presión reducida.

El residuo fue disuelto en tetrahidrofurano (20 mL), y 2-oxo-2-feniletil 4-(hidroximetil)benzoato (0,37 g; 1,4 mmol) y fue agregado 4-dimetilaminopiridina (0,17 g; 1,4 mmol), La solución obtenida fue agitado a temperatura ambiente por 30 min. La mezcla de reacción fue dividida entre acetato de etilo y agua. La capa orgánica fue lavada consecutivamente con 0,1 M de solución de ácido cítrico acuosa, carbonato hidrógeno de sodio acuoso saturado y solución salina saturada, y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar 2-oxo-2-feniletil 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetil}oxi)metil]benzoato (0,63 g; rendimiento 80%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$)δ: 1,02 (9H; s); 1,37 (9H; s); 2,39 (3H; s); 2,49 (3H; s); 2,84 (2H; s); 3,43 (2H; s); 4,08 (2H; d; J = 4,0 Hz); 4,15-4,25 (1H; m); 5,11 (2H; s); 5,59 (2H; s); 6,94 (2H; d; J = 7,9 Hz); 7,17 (2H; d; J = 7,9 Hz); 7,31 (2H; d; J = 8,3 Hz); 7,45-7,55 (2H; m); 7,60-7,70 (1H; m); 7,95-8,00 (2H; m); 8,11 (2H; d; J = 8,3 Hz).

3) El 2-Oxo-2-feniletil 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetil}oxi)metil]benzoato (0,61 g; 0,88 mmol) fue disuelto en acetato de etilo (2 mL) y agua (2 mL),

fue agregado consecutivamente ácido acético (5 mL) y polvo de zinc (0,42 g; 6,4 mmol) a la solución obtenida. La mezcla resultante fue agitadz a 55°C por 24 hrs. La mezcla de reacción fue filtrada y el filtrado fue concentrado bajo presión reducida. El residuo obtenido fue dividido entre acetato de etilo y agua. La capa orgánica fue lavada con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida, y el residuo fue purificado por cromatografía en columna de gel de silice y además recristalizada del hexano-acetato de etilo para dar ácido 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetil}oxi)metil]benzoico (0,29 g; rendimiento 48%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$)δ: 1,02 (9H; s); 1,36 (9H; s); 2,38 (3H; s); 2,47 (3H; s); 2,88 (2H; s); 3,43 (2H; s); 4,10 (2H; d; J = 5,1 Hz); 4,15-4,25 (1H; m); 5,11 (2H; s); 6,94 (2H; d; J = 7,7 Hz); 7,17 (2H; d; J = 7,7 Hz); 7,30 (2H; d; J = 8,1 Hz); 8,07 (2H; d; J = 8,1 Hz).

4) 4-[({[5-(Aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetil}oxi)metil]benzoico dihidrocloruro de ácido (0.22 g; rendimiento 92.4%) fue obtenido como polvo amarillo pálido de 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetil}oxi)metil]benzoico el ácido

(0.25 g; 0.44 mmol) según un método similar al método del Ejemplo 276-3).

1H-RMN (DMSO-d_6)δ: 1.01 (9H, s), 2.37 (3H, s), 2.73 (3H, brs), 3.00-3.30 (2H, m), 3.57 (2H, brs), 3.82 (2H, brs), 5.11 (2H, s), 7.09 (2H, d, J = 7.9 Hz), 7.28 (2H, d, J = 7.9 Hz), 7.34 (2H, d, J = 8.2 Hz), 7.94 (2H, d, J = 8.2 Hz), 8.19 (3H, brs).

Ejemplo 371

Dihidrocloruro de ácido 2-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]furan-3-carboxílico

1) [3-(Metoxicarbonil)-2-furil]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (320 mg, rendimiento 47%) fue obtenido como un aceite incoloro de 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico el ácido (0.50 g; 1.22 mmol) y metilo 2-(bromometil)furan-3-carboxilato (266 mg, 1.22 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,8 Hz); 1,38 (9H; s); 2,15-2,26 (1H; m); 2,37 (3H; s); 2,55 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,82 (3H; s); 4,09-4,13 (2H; m); 4,19 (1H; brs); 5,27 (2H; s); 6,68 (1H; d; J = 1,9 Hz); 7,00 (2H; d; J = 8,1 Hz); 7,11 (2H; d; J = 7,9 Hz); 7,31 (1H; d; J = 1,9 Hz).

2) El ácido 2-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]furan-3-carboxílico (310 mg, rendimiento 99%) fue obtenido como un aceite incoloro de [3-(metoxicarbonil)-2-furil]metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (320 mg; 0,581 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,13-2,22 (1H; m); 2,37 (3H; s); 2,55 (3H; s); 2,80 (2H; d; J = 7,4 Hz); 4,09-4,16 (2H; m); 4,23 (1H; brs); 5,27 (2H; s); 6,72 (1H; d; J = 1,9 Hz); 7,02 (2H; d; J = 7,9 Hz); 7,13 (2H; d; J = 7,4 Hz); 7,34 (1H; d; J = 1,9 Hz).

3) Dihidrocloruro de ácido 2-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]furan-3-carboxílico (241 mg, rendimiento 81%) fue obtenido como un sólido amarillo pálido del ácido 2-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]furan-3-carboxílico (310 mg; 0,577 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,96 (6H; d; J = 6,6 Hz); 2,16-2,25 (1H; m); 2,35 (3H; s); 2,53 (3H; brs); 2,90 (2H; brs); 3,80 (2H; d; J = 5,1 Hz); 5,26 (2H; s); 6,71 (1H; d; J = 1,9 Hz); 7,12 (2H;

d; J = 7,9 Hz); 7,19 (2H; d; J = 7,9 Hz); 7,72 (1H; d; J = 1,9 Hz); 8,32 (3H; brs).

Ejemplo 372

Dihidrocloruro de ácido 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-nitrobenzoico

1) 4-(Metoxicarbonil)-2-nitrobencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (1.91 g; rendimiento 63%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,91 g; 4,63 mmol) y metil 4-(hidroximetil)-3-nitrobenzoato (978 mg; 4,63 mmol) según un método similar al método del Ejemplo 247-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,18-2,28 (1H; m); 2,34 (3H; s); 2,57 (3H; s); 2,79 (2H; d; J = 7,4 Hz); 3,99 (3H; s); 4,10-4,17 (2H; m); 4,23 (1H; brs); 5,41 (2H; s); 7,03-7,09 (3H; m); 7,13 (2H; d; J = 7,9 Hz); 8,08 (1H; dd; J = 8,1; 1,5 Hz); 8,68 (1H; d; J = 1,5 Hz).

2) El ácido 4-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-nitrobenzoico (300 mg, rendimiento 93%) fue obtenido como un aceite incoloro de 4-(metoxicarbonil)-2-nitrobencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-

metilfenil)nicotinato (0,33 g; 0,545 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,18-2,34 (4H; m); 2,59 (3H; s); 2,83 (2H; d; J = 6,8 Hz); 4,10-4,18 (2H; m); 4,26 (1H; brs); 5,42 (2H; s); 7,02-7,20 (5H; m); 8,12-8,16 (1H; m); 8,73 (1H; s).

3) El dihidrocloruro de ácido 4-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-nitrobenzoico (247 mg, rendimiento 86%) fue obtenido como un sólido blanco de ácido 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]-3-nitrobenzoico (300 mg; 0,507 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,97 (6H; d; J = 6,8 Hz); 2,16-2,25 (1H; m); 2,29 (3H; s); 2,60 (3H; brs); 2,94-3,00 (2H; m); 3,81 (2H; d, J = 5,5 Hz); 5,42 (2H; s); 7,17 (4H; s); 7,24 (1H; d; J = 8,1 Hz); 8,13 (1H; dd; J = 8,1; 1,7 Hz); 8,39 (3H; brs); 8,48 (1H; d; J = 1,7 Hz).

Ejemplo 373

Dihidrocloruro de metil 3-{[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxilato

1) El etil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-2-

metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxilato (2,34 g; rendimiento 81%) fue obtenido como un aceite incoloro de terc-butil {[5-(hidroximetil)-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (2,09 g; 5,07 mmol) y etil 3-hidroxi-1-metil-1H-pirazol-4-carboxilato (863 mg; 5,07 mmol) según un método similar al método del Ejemplo 183-1).

^{1}H-RMN ($CDCl_3$) δ:1,03 (9H; s); 1,26-1,28 (3H; m); 1,37 (9H; s); 2,36 (3H; s); 2,66 (3H; s); 2,86 (2H; s); 3,68 (3H; s); 4,13 (1H; brs); 4,23 (2H; q; J = 7,1 Hz); 4,90 (2H; s); 7,11 (2H; d; J = 8,3 Hz); 7,16 (2H; d; J = 8,1 Hz); 7,62 (1H; s).

2) El ácido 3-{[5-{[(terc-Butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxílico (2,22 g; rendimiento 99%) fue obtenido como un aceite incoloro del etil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxilato (2,34 g; 4,14 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:1,04 (9H; s); 1,37 (9H; s); 2,35 (3H; s); 2,66 (3H; s); 2,88 (2H; s); 3,70 (3H; s); 4,09-4,18 (2H; m); 4,24 (1H; brs); 4,95 (2H; s); 7,08 (2H; d; J = 7,5 Hz); 7,18 (2H; d; J = 7,7 Hz); 7,68 (1H; s).

3) El metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-2-

metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxilato (480 mg, rendimiento 91%) fue obtenido como un aceite incoloro del ácido 3-{[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxílico (0,51 g; 0,950 mmol) según un método similar al método del Ejemplo 305-3).

^{1}H-RMN ($CDCl_3$) δ:1,03 (9H; s); 1,37 (9H; s); 2,36 (3H; s); 2,66 (3H; s); 2,86 (2H; s); 3,68 (3H; s); 3,76 (3H; s); 4,09-4,17 (2H; m); 4,19 (1H; brs); 4,90 (2H; s); 7,10 (2H; d; J = 8,1 Hz); 7,16 (2H; d; J = 8,1 Hz); 7,62 (1H; s).

4) El dihidrocloruro de metil 3-{[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxilato (349 mg, rendimiento 76%) fue obtenido como un sólido blanco de metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxilato (480 mg; 0,872 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:1,05 (9H; s); 2,38 (3H; s); 2,91 (3H; brs); 3,28 (2H; brs); 3,65 (3H; s); 3,66 (3H; s); 3,89 (2H; brs); 4,90 (2H; s); 7,27 (2H; d; J = 7,9 Hz); 7,33 (2H; d; J = 8,1 Hz); 8,09 (1H; s); 8,32 (3H; brs).

Ejemplo 374

Dihidrocloruro de ácido 3-{[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxílico

El dihidrocloruro de ácido 3-{[5-(Aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxílico (210 mg, rendimiento 76%) fue obtenido como un sólido blanco del ácido 3-{[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxílico (0,29 g; 0,540 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:1,04 (9H; s); 2,38 (3H; s); 2,87 (3H; brs); 3,23 (2H; brs); 3,64 (3H; s); 3,89 (2H; brs); 4,86 (2H; s); 7,27 (2H; d; J = 7,9 Hz); 7,33 (2H; d; J = 7,9 Hz); 8,00 (1H; s); 8,26 (3H; brs).

Ejemplo 375

Dihidrocloruro de 3-{[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxamida

1) Terc-butil {[5-({[4-(aminocarbonil)-1-metil-1H-pirazol-3-il]oxi}metil)-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (110 mg, rendimiento 18%) fue obtenido como un aceite incoloro del ácido 3-{[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1-metil-1H-pirazol-4-

carboxílico (0,60 g; 1,12 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:1,04 (9H; s); 1,37 (9H; s); 2,37 (3H; s); 2,64 (3H; s); 2,87 (2H; s); 3,69 (3H; s); 4,11-4,16 (2H; m); 4,97 (2H; s); 5,24 (1H; brs); 6,43 (1H; brs); 7,01 (2H; d; J = 7,7 Hz); 7,20 (2H; d; J = 8,3 Hz); 7,69 (1H; s).

2) El dihidrocloruro de 3-{[5-(Aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxamida (70,3 mg; rendimiento 67%) fue obtenido como un sólido blanco del terc-butil {[5-({[4-(aminocarbonil)-1-metil-1H-pirazol-3-il]oxi}metil)-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (110 mg; 0,205 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:1,04 (9H; s); 2,38 (3H; s); 2,91 (3H; brs); 3,25 (2H; brs); 3,63 (3H; s); 3,88 (2H; brs); 4,92 (2H; s); 6,35 (1H; brs); 7,09 (1H; brs); 7,27 (2H; d; J = 7,0 Hz); 7,34 (2H; d; J = 7,5 Hz); 7,91 (1H; s); 8,29 (3H; brs).

Ejemplo 376

Dihidrocloruro de ácido {2-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]fenil}acético

1) El 2-(2-etoxi-2-oxoetil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-

metilfenil)nicotinato (980 mg, rendimiento 70%) fue obtenido como un aceite incoloro de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (1,00 g; 2,42 mmol) y etilo [2-(bromometil)fenil]acetato (624 mg; 2,42 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$)δ:0,96 (6H; d; J = 6,8 Hz); 1,20 (3H; t; J = 7,2 Hz); 1,38 (9H; s); 2,15-2,26 (1H; m); 2,35 (3H; s); 2,51 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,51 (2H; s); 4,02-4,09 (2H; m); 4,09-4,13 (2H; m); 4,19 (1H; brs); 5,02 (2H; s); 6,99 (2H; d; J = 8,3 Hz); 7,06-7,08 (3H; m); 7,16-7,21 (2H; m); 7,26-7,31 (1H; m).

2) El ácido {2-[({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]fenil}acético (600 mg, rendimiento 62%) fue obtenido como un aceite incoloro de 2-(2-etoxi-2-oxoetil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (980 mg; 1,71 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$)δ:0,93 (6H; d; J = 6,8 Hz); 1,37 (9H; s); 2,10-2,21 (1H; m); 2,34 (3H; s); 2,49 (3H; s); 2,76 (2H; d; J = 7,2 Hz); 3,53 (2H; s); 4,05-4,13 (2H; m); 4,29 (1H; brs); 5,01 (2H; s); 6,98 (2H; d; J = 8,3 Hz); 7,02-7,11 (3H; m); 7,18-7,32 (3H; m).

3) El dihidrocloruro de ácido {2-[({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]fenil}acético (125 mg, rendimiento 62%) fue obtenido como un sólido blanco de ácido {2-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]fenil}acético (210 mg; 0,374 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,96 (6H; d; J = 6,6 Hz); 2,16-2,28 (1H; m); 2,36 (3H; s); 2,88 (2H; brs); 3,47 (2H; s); 3,81 (2H; d; J = 5,1 Hz); 4,99 (2H; s); 6,98 (1H; d; J = 7,5 Hz); 7,13-7,32 (7H; m); 8,27 (3H; brs).

Ejemplo 377

Dihidrocloruro de 2-(2-amino-2-oxoetil)bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato

1) 2-(2-amino-2-oxoetil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (323 mg, rendimiento 83%) fue obtenido como un aceite incoloro de ácido {2-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbonil}oxi)metil]fenil}acético (0,39 g; 0,695 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$)δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,13-

2,26 (1H; m); 2,35 (3H; s); 2,50 (3H; s); 2,76 (2H; d; J = 7,4 Hz); 3,47 (2H; s); 4,06-4,13 (2H; m); 4,24 (1H; brs); 5,01 (2H; s); 6,99 (2H; d; J = 8,1 Hz); 7,06-7,10 (3H; m); 7,19-7,35 (3H; m).

2) Dihidrocloruro de 2-(2-amino-2-oxoetil)bencil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (209 mg, rendimiento 68%) fue obtenido como un sólido blanco de 2-(2-amino-2-oxoetil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotinato (323 mg; 0,577 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,96 (6H; d; J = 6,6 Hz); 2,14-2,25 (1H; m); 2,36 (3H; s); 2,55 (3H; s); 2,93 (2H; brs); 3,32 (2H; s); 3,82 (2H; d; J = 5,1 Hz); 5,08 (2H; s); 6,94 (2H; d; J = 7,4 Hz); 7,14-7,30 (7H; m); 7,51 (1H; brs); 8,35 (3H; brs).

Ejemplo 378

Dihidrocloruro de metil 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}tiofen-2-carboxilato

1) El metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}tiofen-2-carboxilato (460 mg, rendimiento 68%) fue obtenido como un aceite incoloro del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,50 g; 1,25 mmol) y metil 3-hidroxitiofen-2-carboxilato (0,20 g;

1,25 mmol) según un método similar al método del Ejemplo 214-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,8 Hz); 1,39 (9H; s); 2,18-2,27 (1H; m); 2,38 (3H; s); 2,72 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,80 (3H; s); 4,06-4,11 (2H; m); 4,20 (1H; brs); 4,79 (2H; s); 6,50 (1H; d; J = 5,5 Hz); 7,06 (2H; d; J = 8,1 Hz); 7,18 (2H; d; J = 7,9 Hz); 7,29 (1H; d; J = 5,5 Hz).

2) El dihidrocloruro de metil 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}tiofen-2-carboxilato (126 mg, rendimiento 84%) fue obtenido como un sólido blanco de metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}tiofen-2-carboxilato (158 mg; 0,293 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,4 Hz); 2,15-2,28 (1H; m); 2,37 (3H; s); 2,88 (3H; s); 3,11 (2H; brs); 3,71 (3H; s); 3,82 (2H; s); 4,87 (2H; s); 6,86 (1H; d; J = 5,7 Hz); 7,21-7,34 (4H; m); 7,77 (1H; d; J = 5,5 Hz); 8,36 (3H; brs).

Ejemplo 379

Dihidrocloruro de metil 4-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-metil-1,3-tiazol-5-carboxilato

1) El etil 4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-

isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-metil-1,3-tiazol-5-carboxilato (910 mg, rendimiento 96%) fue obtenido como un aceite incoloro del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (0,66 g; 1,66 mmol) y etil 4-hidroxi-2-metil-1,3-tiazol-5-carboxilato (0,31 g; 1,66 mmol) según un método similar al método del Ejemplo 214-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,28 (3H; t; J = 7,2 Hz); 1,39 (9H; s); 2,17-2,26 (1H; m); 2,37 (3H; s); 2,53 (3H; s); 2,77 (2H; d; J = 7,2 Hz); 4,08 (2H; d; J = 4,5 Hz); 4,25 (2H; q; J = 7,0 Hz); 5,13 (2H; s); 7,09 (2H; d; J = 8,1 Hz); 7,16 (2H; d; J = 7,9 Hz).

2) El ácido 4-{[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-metil-1,3-tiazol-5-carboxílico (750 mg, rendimiento 87%) fue obtenido como un aceite incoloro del etil 4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-metil-1,3-tiazol-5-carboxilato (910 mg; 1,60 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,18-2,30 (1H; m); 2,38 (3H; s); 2,57 (3H; s); 2,81 (3H; brs); 2,95 (2H; d; J = 7,0 Hz); 4,09-4,15 (2H; m); 4,31 (1H; brs); 5,22 (2H; s); 7,05 (2H; d; J = 7,9 Hz); 7,22 (2H; d; J = 7,9

Hz).

3) El metil 4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-metil-1,3-tiazol-5-carboxilato (420 mg, rendimiento 77%) fue obtenido como un sólido amarillo pálido del ácido 4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-metil-1,3-tiazol-5-carboxílico (530 mg; 0,982 mmol) según un método similar al método del Ejemplo 305-3).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,15-2,27 (1H; m); 2,37 (3H; s); 2,54 (3H; s); 2,68 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,79 (3H; s); 4,08 (2H; d; J = 4,9 Hz); 4,21 (1H; brs); 5,14 (2H; s); 7,09 (2H; d; J = 8,1 Hz); 7,16 (2H; d; J = 7,9 Hz).

4) El dihidrocloruro de metil 4-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-metil-1,3-tiazol-5-carboxilato (342 mg, rendimiento 85%) fue obtenido como un sólido amarillo pálido de metil 4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-metil-1,3-tiazol-5-carboxilato (420 mg; 0,759 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,6 Hz); 2,13-2,28 (1H; m); 2,38 (3H; s); 2,55 (3H; s); 2,93 (3H; brs); 3,13 (2H; brs);

3,70 (3H; s); 3,80 (2H; brs); 5,17 (2H; s); 7,20-7,26 (2H; m); 7,31 (2H; d; J = 7,4 Hz); 8,38 (3H; brs).

Ejemplo 380

Dihidrocloruro de ácido 4-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-metil-1,3-tiazol-5-carboxílico

El dihidrocloruro de ácido 4-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-metil-1,3-tiazol-5-carboxílico (145 mg, rendimiento 69%) fue obtenido como un sólido blanco del ácido 4-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-2-metil-1,3-tiazol-5-carboxílico (220 mg; 0,408 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,6 Hz); 2,15-2,28 (1H; m); 2,38 (3H; s); 2,53 (3H; s); 2,90 (3H; brs); 3,10 (2H; brs); 3,75-3,85 (2H; m); 5,11 (2H; s); 7,25 (2H; d; J = 6,4 Hz); 7,32 (2H; d; J = 7,7 Hz); 8,15-8,42 (3H; m).

Ejemplo 381

Dihidrocloruro de ácido 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-(carboximetil)-1H-pirazol-4-carboxílico

1) El etil 1-acetil-3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1H-pirazol-4-carboxilato

(1,12 g; rendimiento 77%) fue obtenido como un sólido blanco del terc-butil {[5-(hidroximetil)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (1,00 g; 2,51 mmol) y etil 1-acetil-3-hidroxi-1H-pirazol-4-carboxilato (597 mg; 3,01 mmol) según un método similar al método del Ejemplo 214-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,8 Hz); 1,31 (3H; t; J = 7,2 Hz); 1,39 (9H; s); 2,14-2,27 (1H; m); 2,36 (3H; s); 2,51 (3H; s); 2,67 (3H; s); 2,78 (2H; d; J = 7,4 Hz); 4,09 (2H; d; J = 5,1 Hz); 4,20 (1H; brs); 4,28 (2H; q; J = 7,1 Hz); 5,01 (2H; s); 7,09 (2H; d; J = 8,1 Hz); 7,17 (2H; d; J = 7,9 Hz); 8,49 (1H; s).

2) A una solución de etil 1-acetil-3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1H-pirazol-4-carboxilato (0,86 g; 1,49 mmól) en tetrahidrofurano (10 mL) - metanol (5 mL) fue agregado carbonato hidrógeno de sodio acuoso saturado (10 mL) y la mezcla fue agitada a la temperatura ambiente por 30 min. La mezcla de reacción fue diluida con acetato de etilo, fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar etil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1H-pirazol-4-carboxilato

(798 mg, rendimiento 99%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,91 (3H; d; J = 6,6 Hz); 0,97 (3H; d; J = 6,6 Hz); 1,24-1,29 (3H; m); 1,40-1,46 (9H; m); 2,19-2,28 (1H; m); 2,36 (3H; brs); 2,65-2,78 (5H; m); 3,87-4,04 (2H; m); 4,08-4,35 (5H; m); 4,87 (1H; brs); 6,91-7,01 (2H; m); 7,07-7,15 (2H; m); 7,84 (1H; s).

3) A una solución de etil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1H-pirazol-4-carboxilato (1,09 g; 2,03 mmol) en N,N-dimetilformamida (20 mL) fue agregado hidruro de sodio (60% en aceite, 98 mg; 2,44 mmol) y la mezcla fue agitada a la temperatura ambiente por 30 min. Fue agregado bromoacetato de terc-butilo (0,36 mL; 2,44 mmol) a la mezcla de reacción y la mezcla fue agitada con calentamiento a 60°C por 30 min. La mezcla de reacción fue diluída con acetato de etilo, fue lavada con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar etil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-(2-terc-butoxi-2-oxoetil)-1H-pirazol-4-carboxilato (960 mg, rendimiento 72%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,28 (3H; t; J =

7,1 Hz); 1,39 (9H; s); 1,44 (9H; s); 2,14-2,25 (1H; m); 2,36 (3H; s); 2,66 (3H; s); 2,76 (2H; d; J = 7,4 Hz); 4,08 (2H; d; J = 4,9 Hz); 4,17-4,27 (3H; m); 4,52 (2H; s); 4,91 (2H; s); 7,09 (2H; d; J = 8,1 Hz); 7,16 (2H; d; J = 8,1 Hz); 7,73 (1H; s).

4) A una solución mezcla de etilo 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-(2-terc-butoxi-2-oxoetil)-1H-pirazol-4-carboxilato (960 mg; 1,48 mmol) en tetrahidrofurano (15 mL)-metanol (10 mL) fue agregado solución 1N de hidróxido de sodio acuosa (10 mL) y la mezcla fue calentada bajo reflujo por 1 hr. A la mezcla de reacción se le permitió enfriar a la temperatura ambiente y se acidificó con 0,5N de ácido clorhídrico. La mezcla se extrajo con acetato de etilo, y el extracto fue lavado con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida para dar ácido 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-(carboximetil)-1H-pirazol-4-carboxílico (838 mg, rendimiento 99%) como un aceite. El dihidrocloruro de ácido 3-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-(carboximetil)-1H-pirazol-4-carboxílico (58.2 mg, rendimiento 59%) fue obtenido como un sólido blanco de un aceite (107 mg; 0,189

mmol) obtenido según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,6 Hz); 2,14-2,28 (1H; m); 2,38 (3H; s); 2,82 (3H; brs); 3,04 (2H; brs); 3,76-3,86 (2H; m); 4,77 (2H; s); 4,86 (2H; s); 7,26 (2H; d; J = 8,1 Hz); 7,32 (2H; d; J = 7,9 Hz); 8,04 (1H; s); 8,27 (3H; brs).

Ejemplo 382

Dihidrocloruro de metil 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-(2-metoxi-2-oxoetil)-1H-pirazol-4-carboxilato

1) El metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-(2-metoxi-2-oxoetil)-1H-pirazol-4-carboxilato (560 mg; 0,636 mmol) fue obtenido como un aceite incoloro de ácido 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-(carboximetil)-1H-pirazol-4-carboxílico (870 mg; 1,48 mmol) según un método similar al método del Ejemplo 305-3).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,15-2,25 (1H; m); 2,36 (3H; s); 2,66 (3H; s); 2,76 (2H; d; J = 7,2 Hz); 3,76 (3H; s); 3,77 (3H; s); 4,08 (2H; d; J = 4,7 Hz); 4,22 (1H; brs); 4,65 (2H; s); 4,91 (2H; s); 7,08 (2H; d; J = 8,1 Hz); 7,16 (2H; d; J = 7,9 Hz); 7,74 (1H; s).

2) El dihidrocloruro de metil 3-{[5-(aminometil)-6-

isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-(2-metoxi-2-oxoetil)-1H-pirazol-4-carboxilato (59,8 mg; rendimiento 63%) fue obtenido como un sólido blanco de metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-(2-metoxi-2-oxoetil)-1H-pirazol-4-carboxilato (98,7 mg; 0,166 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,98 (6H; d; J = 6,6 Hz); 2,15-2,28 (1H; m); 2,37 (3H; s); 2,74 (3H; brs); 2,94 (2H; brs); 3,67 (3H; s); 3,68 (3H; s); 4,86 (2H; s); 4,91 (2H; s); 7,23 (2H; d; J = 8,1 Hz); 7,29 (2H; d; J = 8,1 Hz); 8,09-8,19 (4H; m).

Ejemplo 383

Dihidrocloruro de ácido [3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-4-(metoxicarbonil)-1H-pirazol-1-il]acético

1) A una solución de metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-(2-metoxi-2-oxoetil)-1H-pirazol-4-carboxilato (0,46 g; 0,775 mmol) en solución 1N de tetrahidrofurano hidróxido de sodio acuosa fue agregado (1 mL) y la mezcla fue agitada a la temperatura ambiente por 30 min. La mezcla de reacción fue acidificada con 0,5N de ácido clorhídrico y fue extraída con acetato de etilo. El extracto fue lavado con solución salina saturada y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo

presión reducida para dar [3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-4-(metoxicarbonil)-1H-pirazol-1-il]acético ácido (450 mg, rendimiento 99%) como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ:1,03 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,21-2,34 (1H; m); 2,43 (3H; s); 3,02-3,26 (5H; m); 3,76 (3H; s); 4,13-4,19 (2H; m); 4,62 (2H; s); 4,99-5,11 (2H; m); 7,12 (2H; d; J = 7,0 Hz); 7,30 (2H; d; J = 7,5 Hz); 7,68-7,75 (1H; m).

2) El dihidrocloruro de ácido [3-{[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-4-(metoxicarbonil)-1H-pirazol-1-il]acético (42,4 mg; rendimiento 44%) fue obtenido como un sólido blanco de ácido [3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-4-(metoxicarbonil)-1H-pirazol-1-il]acético (100 mg; 0,172 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,14-2,28 (1H; m); 2,38 (3H; s); 2,85 (3H; brs); 3,07 (2H; brs); 3,68 (3H; s); 3,75-3,85 (2H; m); 4,78 (2H; s); 4,90 (2H; s); 7,25 (2H; d; J = 7,9 Hz); 7,31 (2H; d; J = 7,9 Hz); 8,12 (1H; s); 8,31 (3H; brs).

Ejemplo 384

Dihidrocloruro de metil 3-{[5-(aminometil)-6-isobutil-2-

metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-(2-amino-2-oxoetil)-1H-pirazol-4-carboxilato

1) El metil 1-(2-amino-2-oxoetil)-3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1H-pirazol-4-carboxilato (150 mg, rendimiento 37%) fue obtenido como un sólido blanco de ácido [3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-4-(metoxicarbonil)-1H-pirazol-1-il]acético (400 mg; 0,689 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,18-2,29 (1H; m); 2,36 (3H; s); 2,68 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,78 (3H; s); 4,08 (2H; d; J = 5,1 Hz); 4,22 (1H; brs); 4,54 (2H; s); 4,94 (2H; s); 7,09 (2H; d; J = 8,1 Hz); 7,16 (2H; d; J = 7,9 Hz); 7,74 (1H; s).

2) El dihidrocloruro de metil 3-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-(2-amino-2-oxoetil)-1H-pirazol-4-carboxilato (141 mg, rendimiento 98%) fue obtenido como un sólido blanco de metil 1-(2-amino-2-oxoetil)-3-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1H-pirazol-4-carboxilato (150 mg; 0,259 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,6 Hz); 2,14-2,27 (1H; m);

2,39 (3H; s); 2,86 (3H; brs); 3,09 (2H; brs); 3,67 (3H; s); 3,81 (2H; d; J = 4,7 Hz); 4,58 (2H; s); 4,89 (2H; s); 7,26 (2H; d; J = 8,1 Hz); 7,32 (2H; d; J = 8,1 Hz); 7,58 (1H; s); 8,33 (3H; brs).

Ejemplo 385

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]tereftalamida

1) Terc-butil {[5-{[4-(aminocarbonil)benzoil]amino}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (248 mg, rendimiento 98%) fue obtenido como polvo blanco de ácido 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoico (260 mg; 0,48 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,15-2,29 (1H; m); 2,34 (3H; s); 2,50 (3H; s); 2,79 (2H; brs); 4,13 (2H; brs); 4,37 (1H; brs); 5,84 (1H; brs); 6,33 (1H; brs); 7,05 (2H; d; J = 8,1 Hz); 7,19 (2H; d; J = 8,1 Hz); 7,37 (1H; brs); 7,47 (2H; d; J = 8,1 Hz); 7,73 (2H; d; J = 8,1 Hz).

2) El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]tereftalamida (233 mg, rendimiento 99%) fue obtenido como polvo blanco del terc-butil {[5-{[4-(aminocarbonil)benzoil]amino}-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (248 mg;

0,47 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,01 (6H; d; J = 6,3 Hz); 2,19-2,31 (1H; m); 2,31 (3H; s); 2,61 (3H; s); 3,05 (2H; brs); 3,85 (2H; brs); 7,25 (4H; s); 7,51 (1H; brs); 7,68 (2H; d; J = 8,1 Hz); 7,89 (2H; d; J = 8,1 Hz); 8,09 (1H; brs); 8,37 (3H; brs); 10,16 (1H; brs).

Ejemplo 386

Dihidrocloruro de etil 1-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)piperidin-4-carboxilato

1) El etil 1-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)piperidin-4-carboxilato fue obtenido como un aceite de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) e isonipecotate del etilo (314 mg; 2,0 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):567

2) El dihidrocloruro de etil 1-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)piperidin-4-carboxilato (324 mg, rendimiento 69%) fue obtenido como polvo blanco del aceite obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,98 (6H; d; J = 6,3 Hz); 1,20 (3H; t; J = 6,9 Hz); 1,54-1,59 (2H; m); 2,10-2,28 (1H; m); 2,34 (3H; s); 2,36-2,46 (1H; m); 2,62-2,76 (4H; m); 3,09 (2H; brs); 3,74-3,82 (4H; m); 4,07 (2H; q; J = 6,9 Hz); 7,19 (2H; d; J = 7,5 Hz); 7,26 (2H; d; J = 7,5 Hz); 8,17 (1H; brs); 8,45 (3H; brs).

Ejemplo 387

Dihidrocloruro de etil 2-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)amino]-1,3-oxazol-4-carboxilato

1) El etil 2-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)amino]-1,3-oxazol-4-carboxilato fue obtenido como un aceite de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y etil 2-amino-1,3-oxazol-4-carboxilato (312 mg; 2,0 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):566

2) El dihidrocloruro de etil 2-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)amino]-1,3-oxazol-4-carboxilato (224 mg, rendimiento 48%) fue obtenido como polvo blanco del aceite obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,6 Hz); 1,29 (3H; t; J = 7,2 Hz); 2,13-2,26 (1H; m); 2,29 (3H; s); 2,63 (3H; s); 3,06 (2H; brs); 3,82 (2H; s); 4,27 (2H; q; J = 7,2 Hz); 7,15-7,29 (4H; m); 8,44 (3H; brs); 8,45 (1H; s); 9,32 (1H; brs); 11,14 (1H, brs).

Ejemplo 388

Dihidrocloruro de etil 2-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)amino]-1,3-tiazol-4-carboxilato

1) El etil 2-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)amino]-1,3-tiazol-4-carboxilato fue obtenido como un aceite de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y etil 2-amino-1,3-tiazol-4-carboxilato (344 mg; 2,0 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):582

2) El dihidrocloruro de etil 2-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)amino]-1,3-tiazol-4-carboxilato (282 mg, rendimiento 51%) fue obtenido como polvo blanco del aceite obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:1,00 (6H; d; J = 6,6 Hz); 1,27 (3H; t; J =

7,2 Hz); 2,11-2,30 (1H; m); 2,35 (3H; s); 2,62 (3H; s); 3,06 (2H; brs); 3,81 (2H; s); 4,24 (2H; q; J = 7,2 Hz); 7,21 (2H; d; J = 7,8 Hz); 7,30 (2H; d; J = 7,8 Hz); 7,91 (1H; s); 8,42 (3H; s); 8,76 (1H; brs); 11,21 (1H; brs).

Ejemplo 389

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-fenilpiperidin-1-carboxamida

1) El terc-butil [(2-isobutil-6-metil-4-(4-metilfenil)-5-{[(4-fenilpiperidin-1-il)carbonil]amino}piridin-3-il)metil]carbamato fue obtenido como un aceite de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y 4-fenilpiperidina (322 mg; 2,0 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):571

2) El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-4-fenilpiperidin-1-carboxamida (240 mg, rendimiento 44%) fue obtenido como polvo blanco del aceite obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,6 Hz); 1,54-1,58 (2H; m); 2,14-2,26 (1H; m); 2,26 (3H; s); 2,50 (3H; s); 2,58-2,75 (5H; m); 3,12 (2H; brs); 3,82 (2H; brs); 3,95-3,99 (2H; m); 7,11-7,37 (9H; m); 8,19 (1H; brs); 8,44 (1H; brs).

Ejemplo 390

Dihidrocloruro de metil 1-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)pirrolidin-2-carboxilato

1) El metil 1-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)pirrolidin-2-carboxilato fue obtenido como un aceite de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y metil éster de DL-prolina (286 mg; 2,0 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):539

2) El dihidrocloruro de metil 1-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)pirrolidin-2-carboxilato (400 mg, rendimiento 78%) fue obtenido como polvo blanco del aceite obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,98 (6H; d; J = 6,6 Hz); 1,80 (3H; brs); 2,04-2,09 (1H; m); 2,11-2,23 (1H; m); 2,39 (3H; s); 2,63 (2H; s); 3,07 (4H; brs); 3,59 (3H; s); 3,86 (2H; brs); 4,11-4,17 (1H; m); 4,11-4,17 (1H; m); 7,21 (2H; d; J = 7,8 Hz); 7,32 (2H; d; J = 7,8 Hz); 7,93 (1H; brs); 8,39 (3H; brs).

Ejemplo 391

Dihidrocloruro de etil 1-({[5-(aminometil)-6-isobutil-2-

metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)piperidin-3-carboxilato

1) El etil 1-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)piperidin-3-carboxilato fue obtenido como un aceite de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y etil 3-piperidincarboxilato (314 mg; 2,0 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):567

2) El dihidrocloruro de etil 1-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)piperidin-3-carboxilato (256 mg, rendimiento 48%) fue obtenido como polvo blanco del aceite obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,98 (6H; d; J = 6,6 Hz); 1,19 (3H; t; J = 6,9 Hz); 1,39-1,46 (2H; m); 1,78 (2H; brs); 2,16-2,23 (1H; m); 2,37 (3H; s); 2,57 (2H; s); 3,03 (2H; s); 3,66-3,72 (1H; m); 3,82 (2H; brs); 4,05 (2H; q; J = 6,9 Hz); 7,17 (2H; d; J = 8,1 Hz); 7,30 (2H; d; J = 8,1 Hz); 8,11 (1H; brs); 8,29 (3H; brs).

Ejemplo 392

Dihidrocloruro de 2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]tetrahidroimidazo[1,5-a]piridin-

1,3(2H,5H)-diona

1) Terc-butil {[5-(1,3-dioxohexahydroimidazo[1,5-a]pyridin-2(3H)-il)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato fue obtenido como un aceite de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y etil 2-piperidincarboxilato (314 mg; 2,0 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):553

2) El dihidrocloruro de 2-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]tetrahidroimidazo[1,5-a]piridin-1,3(2H,5H)-diona (282 mg, rendimiento 57%) fue obtenido como polvo blanco del aceite obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,6 Hz); 1,20-1,35 (1H; m); 1,36-1,50 (1H; m); 1,59-1,65 (1H; m); 1,79 (1H; brs); 1,99 (1H; brs); 2,22-2,31 (1H; m); 2,32 (6H; s); 2,35 (3H; s); 2,70-2,74 (1H; m); 2,82 (2H; d; J = 6,9 Hz); 3,72-3,78 (4H; m), 7,05-7,09 (2H; m); 7,10-7,27 (2H; m); 8,13 (3H; brs).

Ejemplo 393

Dihidrocloruro de 2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-10,10a-dihidroimidazo[1,5-b]isoquinolin-1,3(2H,5H)-diona

1) El terc-butil {[5-(1,3-dioxo-1,5,10,10a-

tetrahidroimidazo[1,5-b]isoquinolin-2(3H)-il)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato fue obtenido como un aceite de ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y etil 1,2,3,4-tetrahidroisoquinolin-3-carboxilato (410 mg; 2,0 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):569

2) El dihidrocloruro de 2-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-10,10a-dihidroimidazo[1,5-b]isoquinolin-1,3(2H,5H)-diona (368 mg, rendimiento 68%) fue obtenido como polvo blanco del aceite obtenido en el 1) mencionado precedentemente, según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ:0,99 (6H; d; J = 6,6 Hz); 2,18-2,34 (1H; m); 2,30 (3H; s); 2,34 (3H; s); 2,34 (2H; d; J = 7,2 Hz); 2,95 (1H; dd; J = 9,9; 17,1 Hz); 3,16 (1H; dd; J = 4,8; 15,6 Hz); 3,78 (2H; m); 4,06 (1H; dd; J = 9,9; 4,8 Hz); 4,08 (1H; d, J = 17,1 Hz); 4,79 (1H; d; J = 15,6 Hz); 7,07-7,31 (8H; m), 8,18 (3H; brs).

Ejemplo 394

Dihidrocloruro de metil 2-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoato

El dihidrocloruro de metil 2-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-

il]amino}carbonil)benzoato (230 mg, rendimiento 89%) fue obtenido como polvo blanco de terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y metil 2-(chlorocarbonil)benzoato (149 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,18-2,27 (1H; m); 2,40 (3H; s); 2,66 (3H; s); 2,95 (2H; brs); 3,77 (3H; s); 3,79 (2H; brs); 6,58 (1H; d; J = 7,5 Hz); 7,23 (2H; d; J = 7,8 Hz); 7,34 (2H; d; J = 7,8 Hz); 7,49 (1H; t; J = 7;5 Hz); 7,53 (1H; t; J = 7,5 Hz); 7,70 (1H; d; J = 7,5 Hz); 8,25 (3H; brs); 10,03 (1H; brs).

Ejemplo 395

Dihidrocloruro de ácido 2-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoico

1) El ácido 2-({[5-[[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoico (247 mg, rendimiento 98%) fue obtenido como polvo blanco de metil 2-({[5-[[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoato (260 mg; 0,48 mmol) según un método similar al método del Ejemplo 36-1).

^{1}H-RMN ($CDCl_3$) δ:0,92 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,04-2,18 (1H; m); 2,41 (3H; s); 2,55 (3H; s); 2,82 (2H; brs);

4,09 (3H; brs); 6,17 (1H; brs); 6,91 (1H; brs); 7,09 (2H; brs); 7,25-7,27 (3H; m); 7,37 (1H; brs); 7,88 (1H; brs).

2) El dihidrocloruro de ácido 2-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoico (220 mg, rendimiento 94%) fue obtenido como polvo blanco de dihidrocloruro de ácido 2-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoico (247 mg; 0,47 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,18-2,26 (1H; m); 2,43 (3H; s); 2,74 (3H; s); 3,05 (2H; brs); 3,86 (2H; brs); 6,38 (1H; d; J = 6,9 Hz); 7,25 (2H; d; J = 8,1 Hz); 7,37 (2H; d; J = 8,1 Hz); 7,41 (1H; t; J = 6,9 Hz); 7,49 (1H; t; J = 6,9 Hz); 7,76 (1H; d; J = 6,9 Hz); 8,35 (3H; brs); 10,02 (1H; brs).

Ejemplo 396

Dihidrocloruro de 2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-1H-isoindol-1,3(2H)-diona

1) Terc-butil ([5-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (221 mg, rendimiento 94%) fue obtenido como polvo blanco de ácido 2-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)benzoico (260 mg; 0,48 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:1,03 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,02 (3H; s); 2,21-2,31 (1H; m); 2,40 (3H; s); 2,83 (2H; d; J = 7,5 Hz); 4,20 (2H; d; J = 5,4 Hz); 4,30 (1H; brs); 6,98 (2H; d; J = 8,1 Hz); 7,03 (2H; d; J = 8,1 Hz); 7,67-7,72 (2H; m); 7,75-7,79 (2H; m).

2) El dihidrocloruro de 2-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-1H-isoindol-1,3(2H)-diona (213 mg, rendimiento 99%) fue obtenido como polvo blanco del terc-butil {[5-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (221 mg; 0,45 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,01 (6H; d; J = 6,3 Hz); 2,19 (3H; s); 2,19-2,32 (1H; m); 2,35 (3H; s); 2,83 (2H; d; J = 6,3 Hz); 3,69 (2H; brs); 7,05 (2H; d; J = 7,8 Hz); 7,13 (2H; d; J = 7,8 Hz); 7,85 (4H; brs); 8,03 (3H; brs).

Ejemplo 397

Dihidrocloruro de metil 3-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)oxi]benzoato

1) El metil 3-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)oxi]benzoato fue obtenido como un aceite del ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-

metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y del metil 3-hidroxibenzoato (304 mg; 2,0 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):562

2) El dihidrocloruro de metil 3-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)oxi]benzoato (172 mg, rendimiento 32%) fue obtenido como un polvo blanco del aceite obtenido del antes mencionado 1), según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,14-2,28 (1H; m); 2,44 (3H; s); 2,67 (3H; s); 3,02 (2H; s); 3,85 (2H; s); 3,89 (3H; s); 7,26 (2H; d; J = 8,1 Hz); 7,36 (1H; s); 7,39 (2H; d; J = 8,1 Hz); 7,53 (1H; t; J = 7,8 Hz); 7,80 (1H; d; J = 7,8 Hz); 8,37 (3H; brs); 9,75 (1H; brs).

Ejemplo 398

Dihidrocloruro de metil 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)oxi]benzoato

1) El metil 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)oxi]benzoato fue obtenido como un aceite del ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y del metil 4-hidroxibenzoato (304 mg; 2,0 mmol) según un método

similar al método del Ejemplo 95-1).

EIMS(M+1):562

2) El dihidrocloruro de metil 4-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)oxi]benzoato (182 mg, rendimiento 34%) fue obtenido como un polvo blanco del aceite obtenido del antes mencionado 1), según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,14-2,29 (1H; m); 2,43 (3H; s); 2,62 (3H; s); 2,93 (2H; brs); 3,84 (2H; s); 3,85 (3H; s); 7,00 (2H; d; J = 8,7 Hz); 7,24 (2H; d; J = 8,1 Hz); 7,39 (2H; d; J = 8,1 Hz); 7,96 (2H; t; J = 8,7 Hz); 8,29 (3H; brs); 9,71 (1H; brs).

Ejemplo 399

Dihidrocloruro de metil 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbamato

1) metil 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]carbamato fue obtenido como un aceite del ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y metanol (62 mg; 2,0 mmol) según un método similar al método del Ejemplo 95-1).

EIMS(M+1):443

2) Dihidrocloruro de metil 5-(aminometil)-6-isobutil-2-metil-

4-(4-metilfenil)piridin-3-il]carbamato (330 mg, rendimiento 80%) fue obtenido como un polvo blanco del aceite obtenido del antes mencionado 1), según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,11-2,18 (1H; m); 2,39 (3H; s); 2,63 (3H; s); 3,11 (2H; s); 3,48 (3H; s); 3,82 (2H; s); 7,18 (2H; d; J = 7,8 Hz); 7,33 (2H; d; J = 7,8 Hz); 8,44 (3H; brs); 9,03 (1H; brs),

Ejemplo 400

Dihidrocloruro de etil {3-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2,4-dioxoimidazolidin-1-il}acetato

1) El dietil 2,2'-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)imino]diacetato fue obtenido como cristales blancos (260 mg, rendimiento 43%) del ácido 5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)nicotínico (412 mg; 1,0 mmol) y del dietil 2,2'-iminodiacetato (380 mg; 2,0 mmol) según un método similar al método del Ejemplo 95-1).

^{1}H-RMN ($CDCl_3$)δ:0,96 (6H; d; J = 6,6 Hz); 1,24 (6H; t; J = 6,9 Hz); 1,38 (9H; s); 2,09-2,24 (1H; m); 2,40 (3H; s); 2,49 (3H; s); 2,75 (2H; d; J = 6,9 Hz); 3,87 (4H; s); 4,12 (4H; q; J = 6,9 Hz); 4,23 (1H; brs); 6,33 (1H; brs); 7,04 (2H; d; J = 7,8

Hz); 7,25 (2H; d; J = 7,8 Hz).

2) El dihidrocloruro de etil {3-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-2,4-dioxoimidazolidin-1-il}acetato (240 mg, rendimiento 98%) fue obtenido como un polvo blanco del dietil 2,2'-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)imino]diacetato (260 mg; 0,43 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 1,19 (6H; t; J = 7,2 Hz); 2,22-2,35 (1H; m); 2,35 (3H; s); 2,50 (3H; s); 2,86 (2H; d; J = 7,2 Hz); 3,74-3,80 (3H; m); 4,02-4,17 (5H; m); 7,04-7,11 (2H; m); 7,21-7,27 (2H; m); 8,25 (3H; brs).

Ejemplo 401

Dihidrocloruro de Etil 6-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)piridina-2-carboxilato

Dihidrocloruro de etil 6-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)piridina-2-carboxilato (230 mg, rendimiento 89%) fue obtenido como un polvo blanco de terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y del etil 6-(clorocarbonil)piridina-2-carboxilato (149 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 1,35 (3H; t; J =

7,2 Hz); 2,11-2,28 (1H; m); 2,27 (3H; s); 2,60 (3H; s); 3,05 (2H; brs); 3,84 (2H; brs); 4,37 (2H; q; J = 7,2 Hz); 7,22 (1H; d; J = 7,8 Hz); 7,26 (2H; d; J = 7,8 Hz); 8,21-8,31 (3H; m); 8,38 (3H; brs); 9,90 (1H, brs).

Ejemplo 402

Dihidrocloruro ácido de 6-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)piridina-2-carboxílico

1) El ácido 6-({[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)piridina-2-carboxílico (247 mg, rendimiento 98%) fue obtenido como un polvo blanco del etil 6-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)piridina-2-carboxilato (260 mg; 0,48 mmol) según un método similar al método del Ejemplo 36-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,14-2,26 (1H; m); 2,28 (3H; s); 2,52 (3H; s); 2,84 (2H; brs); 4,15 (2H; s); 4,42 (1H; brs); 7,01 (2H; d; J = 7,8 Hz); 7,10 (2H; d; J = 7,8 Hz); 7,99 (1H; brs); 8,21-8,31 (2H; m); 9,36 (1H, brs).

2) Dihidrocloruro ácido de 6-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)piridina-2-carboxílico (221 mg, rendimiento 94%) fue obtenido como un polvo blanco del ácido 6-({[5-{[(terc-

butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)piridina-2-carboxílico (247 mg; 0,47 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,11-2,29 (1H; m); 2,25 (3H; s); 2,60 (3H; s); 3,04 (2H; brs); 3,85 (2H; brs); 7,19 (1H; d; J = 7,8 Hz); 7,26 (2H; d; J = 7,8 Hz); 8,17-8,26 (3H; m); 8,37 (3H; brs); 10,67 (1H; brs).

Ejemplo 403

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]piridina-2,6-dicarboxamida

1) Terc-butil {[5-({[6-(aminocarbonil)piridin-2-il]carbonil}amino)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (221 mg, rendimiento 94%) fue obtenido como un polvo blanco del ácido 6-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]amino}carbonil)piridina-2-carboxílico (260 mg; 0,48 mmol) según un método similar al método del Ejemplo 3-1).

^{1}H-RMN ($CDCl_3$) δ:1,00 (6H; d; J = 6,6 Hz); 1,39 (9H; s); 2,18-2,29 (1H; m); 2,35 (3H; s); 2,57 (3H; s); 2,79 (2H; d; J = 7,5 Hz); 4,15 (2H; brs); 4,29 (1H; brs); 5,53 (1H; brs); 6,75 (1H; brs); 7,07 (2H; d; J = 7,8 Hz); 7,19 (2H; d; J = 7,8 Hz); 8,02 (1H; t; J = 7,8 Hz); 8,29 (1H; dd; J = 1,2; 7,8

Hz); 8,31 (1H; dd; J = 1,2; 7,8 Hz); 8,74 (1H; s).

2) Dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]piridina-2,6-dicarboxamida (206 mg, rendimiento 94%) fue obtenido como un polvo blanco del terc-butil {[5-({[6-(aminocarbonil)piridin-2-il]carbonil}amino)-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (221 mg; 0,45 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,3 Hz); 2,12-2,28 (1H; m); 2,25 (3H; s); 2,63 (3H; s); 3,07 (2H; brs); 3,86 (2H; brs); 7,19 (2H; d; J = 7,8 Hz); 7,28 (2H; d; J = 7,8 Hz); 7,76 (1H; s); 8,08-8,20 (3H; m); 8,43 (3H; brs); 8,80 (1H; s); 10,77 (1H; brs).

Ejemplo 404

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-1-bencil-4-metoxi-1H-pirazol-3-carboxamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-1-bencil-4-metoxi-1H-pirazol-3-carboxamida (230 mg, rendimiento 81%) fue obtenido como un polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y del cloruro de 1-bencil-4-metoxi-1H-pirazol-3-carbonilo (188 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,18-2,26 (1H; m); 2,35 (3H; s); 2,51 (3H; s); 2,91 (2H; brs); 3,67 (3H; s); 3,81 (2H; brs); 5,15 (2H; s); 7,16-7,39 (9H; m); 8,11 (1H; s); 8,21 (3H; brs).

Ejemplo 405

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-1,5-dimetil-1H-pirazol-3-carboxamida

El dihidrocloruro de N-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-1,5-dimetil-1H-pirazol-3-carboxamida (235 mg, rendimiento 97%) fue obtenido como un polvo blanco del terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (192 mg; 0,5 mmol) y del cloruro de 1,5-dimetil-1H-pirazol-3-carbonilo (118 mg; 0,75 mmol) según un método similar al método del Ejemplo 223.

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,18-2,25 (1H; m); 2,32 (3H; s); 2,33 (3H; s); 2,53 (2H; brs); 3,73 (3H; s); 3,82 (2H; brs); 6,38 (1H; s); 7,20 (2H; d; J = 7,8 Hz); 7,24 (2H; d; J = 7,8 Hz); 8,31 (3H; s); 9,58 (1H; brs).

Ejemplo 406

Dihidrocloruro ácido de [5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetico

El dihidrocloruro de ácido [5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetico (0,56 g, rendimiento 94%) fue obtenido como un polvo blanco del ácido

[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetico (0,63 g; 1,43 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ: 1,03 (9H; s); 2,41 (3H; s); 2,73 (3H; brs); 3,19 (2H; brs); 3,35-3,45 (2H; m); 3,75-3,90 (2H; m); 7,16 (2H; d; J = 7,4 Hz); 7,38 (2H; d; J = 7,4 Hz); 8,16 (3H; brs),

Ejemplo 407

Dihidrocloruro de (5-metil-2-oxo-1,3-dioxol-4-il)metil [5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetato

1) El (5-metil-2-oxo-1,3-dioxol-4-il)metil [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetato (0,091 g; rendimiento 28%) fue obtenido como un polvo blanco del ácido [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acético (0,63 g; 1,43 mmol) según un método similar al método del Ejemplo 176-1).

^{1}H-RMN ($CDCl_3$)δ: 1,02 (9H; s); 1,37 (9H; s); 2,14 (3H; s); 2,40 (3H; s); 2,48 (3H; s); 2,83 (2H; s); 3,39 (2H; s); 4,09 (2H; d; J = 4,9 Hz); 4,10-4,25 (1H; m); 4,76 (2H; s); 6,94 (2H; d; J = 7,9 Hz); 7,21 (2H; d; J = 7,9 Hz).

2) El dihidrocloruro de (5-metil-2-oxo-1,3-dioxol-4-il)metil [5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-

3-il]acetato (0,085 g, rendimiento 99%) fue obtenido como un polvo amarillo pálido del (5-metil-2-oxo-1,3-dioxol-4-il)metil [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]acetato (0,090 g; 0,16 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6)δ: 1,01 (9H; s); 2,14 (3H; s); 2,38 (3H; s); 2,71 (3H; brs); 3,13 (2H; brs); 3,52 (2H; brs); 3,73 (2H; brs); 4,92 (2H; s); 7,10 (2H; d; J = 7,5 Hz); 7,31 (2H; d; J = 7,5 Hz); 8,15 (3H; brs).

Ejemplo 408

Metil 5-(aminometil)-6-isobutil-2-(metoximetil)-4-(4-metilfenil)nicotinato

1) Una mezcla de metil 4-metoxiacetato (5,85 g; 40 mmol), acetato de amonio (15,4 g; 200 mmol), ácido acético (2,3 mL, 40 mmol) y tolueno (100 mL) fue calentada bajo reflujo usando una trampa Dean-Stark durante 10 hrs. A la mezcla de reacción se le permitió enfriarse a temperatura ambiente, fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida para dar metil 3-amino-4-metoxibut-2-enoato como un producto bruto (5,8 g). El metil 5-ciano-6-isobutil-2-(metoximetil)-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (7,8 g; rendimiento 55%) fue obtenido como un polvo amarillo pálido del producto bruto (5,8 g), del 5-metil-3-oxohexanonitrilo (5,7 g; 87.5% de pureza, 40 mmol) y

del p-tolualdehído (4,8 g; 40 mmol) según un método similar al método del Ejemplo 1-2).

^{1}H-RMN ($CDCl_3$)δ: 0,97 (6H; dd; J = 6,6; 12,8 Hz); 1,80-2,00 (1H; m); 2,20-2,40 (2H; m); 2,31 (3H; s); 3,48 (3H; s); 3,57 (3H; s); 4,56 (1H; s); 4,64 (1H; d; J = 16,4 Hz); 4,73 (1H; d; J = 16,4 Hz); 7,05-7,15 (5H; m).

2) El metil 5-ciano-6-isobutil-2-(metoximetil)-4-(4-metilfenil)nicotinato (7,5 g; rendimiento 99%) fue obtenido como un polvo blanco del metil 5-ciano-6-isobutil-2-(metoximetil)-4-(4-metilfenil)-1,4-dihidropiridin-3-carboxilato (7,7 g; 22 mmol) según un método similar al método del Ejemplo 23-3).

^{1}H-RMN ($CDCl_3$)δ: 1,00 (6H; d; J = 6,6 Hz); 2,20-2,35 (1H; m); 2,41 (3H; s); 2,97 (2H; d; J = 7,2 Hz); 3,37 (3H; s); 3,59 (3H; s); 4,71 (2H; s); 7,15-7,35 (4H; m).

3) El Metil 5-(aminometil)-6-isobutil-2-(metoximetil)-4-(4-metilfenil)nicotinato (7,1 g; rendimiento 93%) fue obtenido como un aceite amarillo pálido del metil 5-ciano-6-isobutil-2-(metoximetil)-4-(4-metilfenil)nicotinato (7,4 g; 21 mmol) según un método similar al método del Ejemplo 1-4).

^{1}H-RMN ($CDCl_3$)δ: 0,97 (6H; d; J = 6,8 Hz); 1,22 (2H; brs); 2,15-2,30 (1H; m); 2,39 (3H; s); 2,82 (2H; d; J = 7,4 Hz); 3,36 (3H; s); 3,49 (3H; s); 3,67 (2H; s); 4,65 (2H; s); 7,11 (2H; d; J = 8,1 Hz); 7,21 (2H; d; J = 8,1 Hz).

Ejemplo 409

Trihidrocloruro de {6-metil-4-(4-metilfenil)-2-neopentil-5-[(piridin-2-iltio)metil]piridin-3-il}metilamina

1) El terc-butil ({6-metil-4-(4-metilfenil)-2-neopentil-5-[(piridin-2-iltio)metil]piridin-3-il}metil)carbamato (480 mg, rendimiento 78%) fue obtenido como un polvo del metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metil (600 mg, 1,2 mmol) y del 2-mercaptopiridina (145 mg; 1,3 mmol) según un método similar al método del Ejemplo 33-1).

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,37 (9H; s); 2,35 (3H; s); 2,62 (3H; s); 2,83 (2H; s); 4,08 (2H; d; J=4,9 Hz); 4,14 (2H; s); 4,19 (1H; s); 6,91-6,95 (1H; m); 7,03-7,06 (3H; m); 7,17 (2H; d; J=7,91 Hz); 7,39-7,45 (1H; m); 8,31 (1H; d; J=4,1 Hz).

2) El trihidrocloruro de {6-metil-4-(4-metilfenil)-2-neopentil-5-[(piridin-2-iltio)metil]piridin-3-il}metilamina (167 mg, rendimiento 82%) fue obtenido como polvo del terc-butil ({6-metil-4-(4-metilfenil)-2-neopentil-5-[(piridin-2-iltio)metil]piridin-3-il}metil)carbamato (200 mg; 0,395 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,03 (9H; s); 2,36 (3H; s); 2,90 (3H; s); 3,28 (2H; s); 3,83 (2H; d; J=4,7 Hz); 4,19 (2H; s); 7,11-7,16 (1H; m); 7,23-7,33 (5H; m); 7,62-7,67 (1H; m); 8,31 (3H;

brs); 8,33-8,34 (1H; m).

Ejemplo 410

Dihidrocloruro de {6-metil-4-(4-metilfenil)-2-neopentil-5-[(1H-1,2,4-triazol-3-iltio)metil]piridin-3-il}metilamina

1) El terc-butil ({6-metil-4-(4-metilfenil)-2-neopentil-5-[(4H-1,2,4-triazol-3-iltio)metil]piridin-3-il}metil)carbamato (455 mg, rendimiento 2%) fue obtenido como un polvo del metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metil (600 mg; 1,2 mmol) y del 3-mercapto-1,2,4-triazol (131 mg; 1,3 mmol) según un método similar al método del Ejemplo 33-1).

^{1}H-RMN ($CDCl_3$) δ:1,01 (9H; s); 1,37 (9H; s); 2,37 (3H; s); 2,64 (3H; s); 2,83 (2H; s); 4,08 (2H; d; J=4,9 Hz); 4,12 (2H; s); 4,22 (1H; s); 7,04 (2H; d; J=7,7 Hz); 7,20 (2H; d; J=7,7 Hz); 8,02 (1H; s).

2) Dihidrocloruro de {6-metil-4-(4-metilfenil)-2-neopentil-5-[(1H-1,2,4-triazol-3-iltio)metil]piridin-3-il}metilamina (160 mg, rendimiento 85%) fue obtenido como un polvo del terc-butil ({6-metil-4-(4-metilfenil)-2-neopentil-5-[(4H-1,2,4-triazol-3-iltio)metil]piridin-3-il}metil)carbamato (200 mg; 0,403 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,02 (9H; s); 2,39 (3H; s); 2,86 (3H; s); 3,21 (2H; s); 3,81 (2H; d; J=4,1 Hz); 4,08 (2H; s); 7,24 (2H;

d; J=8,0 Hz); 7,35 (2H; m; J=8,0 Hz); 8,23 (3H; brs); 8,45 (1H; s).

Ejemplo 411

Trihidrocloruro de [5-[(1H-imidazol-2-iltio)metil]-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metilamina

1) El terc-butil {[5-[(1H-imidazol-2-iltio)metil]-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (373 mg, rendimiento 75%) fue obtenido como polvo del metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metilo (500 mg; 1,0 mmol) y del 2-mercaptoimidazol (110 mg; 1,1 mmol) según un método similar al método del Ejemplo 33-1).

^{1}H-RMN ($CDCl_3$) δ:1,01 (9H; s); 1,37 (9H; s); 2,41 (3H; s); 2,55 (3H; s); 2,82 (2H; s); 3,94 (2H; s); 4,06 (2H; d; J=4,9 Hz); 4,20 (1H; s); 6,94 (1H; brs); 7,01 (2H; d; J=7,9 Hz); 7,06 (1H; brs); 7,23 (2H; d; J=7,9 Hz).

2) El Trihidrocloruro de [5-[(1H-Imidazol-2-iltio)metil]-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metilamina (160 mg, rendimiento 79%) fue obtenido como un polvo del terc-butil {[5-[(1H-imidazol-2-iltio)metil]-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (200 mg; 0,404 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,01 (9H; s); 2,40 (3H; s); 2,67 (3H; s);

3,07 (2H; brs); 3,74 (2H; brs); 4,17 (2H; s); 7,18 (2H; d; J=7,9 Hz); 7,33 (2H; d; J=7,9 Hz); 7,70 (2H; s); 8,26 (3H; brs).

Ejemplo 412

Trihidrocloruro de {6-metil-4-(4-metilfenil)-2-neopentil-5-[(pirimidin-2-iltio)metil]piridin-3-il}metilamina.

1) Terc-butil ({6-metil-4-(4-metilfenil)-2-neopentil-5-[(pirimidin-2-iltio)metil]piridin-3-il}metil)carbamato (380 mg, rendimiento 77%) fue obtenido como un polvo del metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metilo (500 mg; 1,0 mmol) y del 2-mercaptopirimidina (123 mg; 1,1 mmol) según un método similar al método del Ejemplo 33-1).

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,37 (9H; s); 2,35 (3H; s); 2,65 (3H; s); 2,83 (2H; s); 4,08 (2H; d; J=4,9 Hz); 4,14 (2H; s); 4,19 (1H; brs); 6,92 (1H; t; J=4,9 Hz); 7,06 (2H; d; J=7,8 Hz); 7,18 (2H; d; J=7,8 Hz); 8,43 (2H; d; J=4,9 Hz).

2) El trihidrocloruro de {6-metil-4-(4-metilfenil)-2-neopentil-5-[(pirimidin-2-iltio)metil]piridin-3-il}metilamina (180 mg, rendimiento 88%) fue obtenido como un polvo del terc-butil ({6-metil-4-(4-metilfenil)-2-neopentil-5-[(pyrimidin-2-iltio)metil]piridin-3-il}metil)carbamato (200 mg; 0,395 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,02 (9H; s); 2,35 (3H; s); 2,85 (3H; s);

3,17 (2H; brs); 3,80 (2H; s); 4,18 (2H; s); 7,21-7,13 (5H; m); 8,22 (3H; brs); 8,57 (2H; d; J=4,9 Hz).

Ejemplo 413

Trihidrocloruro de [5-{[(5-metoxi-1H-benzimidazol-2-il)tio]metil}-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metilamina

1) El terc-butil {[5-{[(5-metoxi-1H-benzimidazol-2-il)tio]metil}-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (530 mg, rendimiento 92%) fue obtenido como un polvo del metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metilo (500 mg; 1,0 mmol) y del 5-metoxi-2-benzimidazoletilo (198 mg; 1,1 mmol) según un método similar al método del Ejemplo 33-1).

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,37 (9H; s); 2,33 (3H; s); 2,64 (3H; s); 2,83 (2H; s); 3,82 (3H; s); 4,07 (2H; d; J=5,1 Hz); 4,22 (2H; s); 4,25 (1H; s); 6,77-6,84 (2H; m); 7,01 (2H; d; J=7,9 Hz); 7,14-7,16 (3H; m); 7,49 (1H; d; J=8,9 Hz).

2) El trihidrocloruro de [5-{[(5-Metoxi-1H-benzimidazol-2-il)tio]metil}-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metilamina (194 mg, rendimiento 91%) fue obtenido como un polvo del terc-butil {[5-{[(5-metoxi-1H-benzimidazol-2-il)tio]metil}-6-metil-4-(4-metilfenil)-2-neopentilpiridin-3-il]metil}carbamato (200 mg; 0,365 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,02 (9H; s); 2,30 (3H; s); 2,83 (3H; s); 3,12 (2H; brs); 3,77 (2H; s); 3,81 (3H; s); 4,37 (2H; s); 6,94-7,02 (2H; m); 7,20-7,27 (4H; m); 7,46 (1H; d; J=8,9 Hz); 8,23 (3H; brs).

Ejemplo 414

Dihidrocloruro de metil 3-{[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1H-pirazol-5-carboxilato

1) El metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1H-pirazol-5-carboxilato (800 mg, rendimiento 52%) fue obtenido como un polvo del metansulfonato de [5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metilo (1,4 g; 2,85 mmol) y del metil 3-hidroxi-1H-pirazol-5-carboxilato (426 mg; 3,0 mmol) según un método similar al método del Ejemplo 33-1).

^{1}H-RMN ($CDCl_3$) δ:1,02 (9H; s); 1,37 (9H; s); 2,36 (3H; s); 2,62 (3H; s); 2,86 (2H; s); 3,89 (3H; s); 4,13 (2H; d; J=4,5 Hz); 4,20 (1H; brs); 4,84 (2H; s); 6,13 (1H; s); 7,04 (2H; d; J=7,8 Hz); 7,16 (2H; d; J=7,8 Hz); 9,89 (1H; brs).

2) El dihidrocloruro de metil 3-{[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1H-pirazol-5-carboxilato (142 mg, rendimiento 75%) fue obtenido como un polvo del metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-2-

metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi-1H-pirazol-5-carboxilato (200 mg; 0,373 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,03 (9H; s); 2,37 (3H; s); 2,84 (3H; s); 3,23 (2H; brs); 3,81 (3H; s); 3,87 (2H; brs); 4,83 (2H; s); 6,17 (1H; s); 7,25 (2H; d; J=7,9 Hz); 7,33 (1H; d; J=7,9 Hz); 8,29 (3H; brs).

Ejemplo 415

Dihidrocloruro ácido de 3-{[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1H-pirazol-5-carboxílico

1) El ácido 3-{[5-{[(terc-Butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1H-pirazol-5-carboxílico (914 mg, rendimiento 81%) fue obtenido como un sólido blanco del metil 3-{[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1H-pirazol-5-carboxilato (1,16 g; 2,16 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN (DMSO-d_6) δ:1,00 (9H; s); 1,34 (9H; s); 2,32 (3H; s); 2,53 (3H; s); 2,69 (2H; s); 3,87 (2H; d; J=3,2 Hz); 4,73 (2H; s); 6,06 (1H; s); 6,83 (1H; t; J=4,1 Hz); 7,13-7,21 (4H; m); 12,91 (1H; s).

2) El dihidrocloruro ácido de 3-{[5-(Aminometil)-2-metil-4-

(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1H-pirazol-5-carboxílico (180 mg, rendimiento 95%) fue obtenido como un polvo blanco del ácido 3-{[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]metoxi}-1H-pirazol-5-carboxílico (200 mg; 0,383 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,03 (9H; s); 2,37 (3H; s); 2,51 (3H; s); 2,78 (2H; s); 3,85 (2H; s); 4,80 (2H; s); 6,09 (1H; s); 7,23 (2H; d; J=7,9 Hz); 7,32 (2H; d; J=7,9 Hz); 8,16 (3H; brs).

Ejemplo 416

Dihidrocloruro de 4-(metoxicarbonil)bencil 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotinato

1) El 4-(Metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilnicotinato (7,36 g; rendimiento 70%) fue obtenido como un sólido blanco del ácido 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilnicotínico (7,8 g; 18,3 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:1,01 (9H; s); 1,36 (9H; s); 2,35 (3H; s); 2,53 (3H; s); 2,87 (2H; s); 3,93 (3H; s); 4,17 (2H; s); 4,98 (2H; s); 7,02 (2H; d; J=7,9 Hz); 7,09 (2H; d; J=8,2 Hz); 7,11 (2H; d; J=7,9 Hz); 7,93 (2H; d; J=8,2 Hz).

2) El dihidrocloruro de 4-(metoxicarbonil)bencil 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotinato (181 mg, rendimiento 95%) fue obtenido como un polvo blanco del 4-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilnicotinato (200 mg; 0,348 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (9H; s); 2,33 (3H; s); 2,51 (3H; s); 2,90 (2H; s); 3,83 (2H; s); 3,86 (3H; s); 5,07 (2H; s); 7,12-7,21 (6H; m); 7,87 (2H; d; J=8,3 Hz); 8,13 (3H; brs).

Ejemplo 417

Dihidrocloruro ácido 4-[({[5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]carbonil}oxi)metil]benzoico.

1) El ácido 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]carbonil}oxi)metil]benzoico (1,68 g; rendimiento 86%) fue obtenido como un sólido blanco del 4-(metoxicarbonil)bencil 5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilnicotinato (2,0 g; 3,48 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:1,01 (9H; s); 1,37 (9H; s); 2,35 (3H; s); 2,55 (3H; s); 2,89 (2H; s); 4,16-4,20 (3H; m); 5,01 (2H; s); 7,02-7,13 (6H; m); 7,99 (2H; d; J=8,3 Hz).

2) El dihidrocloruro de ácido 4-[({[5-(Aminometil)-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]carbonil}oxi)metil]benzoico (150 mg, rendimiento 79%) fue obtenido como un polvo blanco del ácido 4-[({[5-{[(terc-butoxicarbonil)amino]metil}-2-metil-4-(4-metilfenil)-6-neopentilpiridin-3-il]carbonil}oxi)metil]benzoico (200 mg; 0,357 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (9H; s); 2,34 (3H; s); 2,51 (3H; s); 2,90 (2H; s); 3,84 (2H; d; J=5,7 Hz); 5,06 (2H; s); 7,10-7,18 (6H; m); 7,85 (2H; d; J=8,3 Hz); 8,11 (3H; brs),

Ejemplo 418

Dihidrocloruro de 4-(trifluormetil)bencil [5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato.

1) El 4-(Trifluormetil)bencil [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (350 mg, rendimiento 85%) fue obtenido como un polvo blanco del ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetico (300 mg; 0,703 mmol) y del 1-(bromometil)-4-(trifluormetil)benceno (250 mg; 1,05 mmol) según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,8 Hz); 1,37 (9H; s); 2,11-2,29 (1H; m); 2,37 (3H; s); 2,48 (3H; s); 2,75 (2H; d; J =

6,6 Hz); 3,42 (2H; s); 4,03 (2H; d; J = 5,1 Hz); 4,20 (1H; brs); 5,09 (2H; s); 6,91 (2H; d; J = 7,7 Hz); 7,14 (2H; d; J = 7,7 Hz); 7,33 (2H; d; J = 8,1 Hz); 7,60 (2H; d; J = 8,1 Hz).

2) El dihidrocloruro de 4-(Trifluormetil)bencil [5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (283 mg, rendimiento 66%) fue obtenido como un polvo blanco del 4-(trifluormetil)bencil [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (330 mg; 0,564 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,09-2,25 (1H; m); 2,36 (3H; s); 2,77 (3H; s); 3,12 (2H;s); 3,77 (2H; d; J = 5,1 Hz); 5,14 (2H; s); 7,09 (2H; d; J = 8,1 Hz); 7,24 (2H; d; J = 8,1Hz); 7,47 (2H; d; J = 8,1 Hz); 7,76 (2H; d; J = 8,1 Hz); 8,35 (3H, brs).

Ejemplo 419

Dihidrocloruro de 4-fluorbencil [5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato

1) 4-Fluorbencil [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (325 mg, rendimiento 86%) fue obtenido como un polvo blanco del ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetico (300 mg; 0,703 mmol) y del 1-(bromometil)-4-fluorbenceno (198 mg; 1,05 mmol)

según un método similar al método del Ejemplo 169-1).

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,11-2,26 (1H; m); 2,38 (3H; s); 2,46 (3H; s); 2,74 (2H; d; J = 7,4 Hz); 3,38 (2H; s); 4,02 (2H; d; J = 4,9 Hz); 4,20 (1H; brs); 5,00 (2H; s); 6,90 (2H; d; J = 7,9 Hz); 6,88-7,07 (2H; m); 7,14 (2H; d; J = 7,9 Hz); 7,15-7,25 (2H; m).

2) Dihidrocloruro de 4-Fluorbencil [5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (234 mg, rendimiento 82%) fue obtenido como un polvo blanco del 4-fluorbencil [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetato (300 mg; 0,561 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,12-2,26 (1H; m); 2,38 (3H; s); 2,84 (3H; s); 3,26 (2H; d; J = 6,8 Hz); 3,79 (2H; d; J = 4,5 Hz); 5,03 (2H; s); 7,12 (2H; d; J = 7,9 Hz); 7,17-7,39 (6H; m); 8,57 (3H; brs).

Ejemplo 420

Dihidrocloruro de {[2-isobutil-6-metil-4-(4-metilfenil)-5-(2-oxo-2-pirrolidin-1-iletil)piridin-3-il]metil}amina

1) El terc-butil {[2-isobutil-6-metil-4-(4-metilfenil)-5-(2-oxo-2-pirrolidin-1-iletil)piridin-3-il]metil}carbamato (120 mg, rendimiento 36%) fue obtenido como un polvo blanco del ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-

metil-4-(4-metilfenil)piridin-3-il]acetico (300 mg; 0,703 mmol) y del pirrolinina (440 mg; 2,11 mmol) según un método similar al método del Ejemplo 311-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,37 (9H; s); 2,12-2,25 (1H; m); 2,39 (3H; s); 2,55 (3H; s); 2,74 (2H; d; J = 7,4 Hz); 2,86-2,97 (4H; m); 3,28 (2H; s); 3,36 (2H; t; J = 6,5 Hz); 4,03 (2H; d; J = 4,7 Hz); 4,20 (1H; brs); 7,01 (2H; d; J = 7,9 Hz); 7,21 (2H; d; J = 7,9 Hz).

2) El dihidrocloruro de {[2-isobutil-6-metil-4-(4-metilfenil)-5-(2-oxo-2-pirrolidin-1-iletil)piridin-3-il]metil}amina (62,4 mg, rendimiento 66%) fue obtenido como un polvo blanco del terc-butil {[2-isobutil-6-metil-4-(4-metilfenil)-5-(2-oxo-2-pirrolidin-1-iletil)piridin-3-il]metil}carbamato (100 mg; 0,208 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,11-2,26 (1H; m); 2,40 (3H; s); 2,80 (3H; s); 2,88 (2H; t; J = 6,1 Hz); 3,12-3,29 (4H; m); 3,42 (2H; s); 3,81 (2H; s); 7,17 (2H; d; J = 7,9 Hz); 7,38 (2H; d; J = 7,9 Hz); 8,43 (3H; brs).

Ejemplo 421

Dihidrocloruro de etil 1-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}piperidin-4-carboxilato

1) El etil 1-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-

il]acetil}piperidin-4-carboxilato (330 mg, rendimiento 50%) fue obtenido como un polvo blanco del ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetico (500 mg; 1,17 mmol) y del etil piperidin-4-carboxilato (553 mg; 3,52 mmol) según un método similar al método del Ejemplo 311-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,27 (3H; t; J = 7,2 Hz); 1,37 (9H; s); 1,54 (1H; dd; J = 13,2; 9,8 Hz); 1,64-1,75 (1H; m); 1,87 (1H; dd; J = 13,2; 2;6 Hz); 2,12-2,27 (1H; m); 2,38 (3H; s); 2,49 (3H; s); 2,74 (2H; d; J = 7,2 Hz); 2,81-3,01 (3H; m); 3,30 (2H; s); 3,49-3,60 (1H; m); 4,15 (2H; q; J = 7,2 Hz); 4,20 (1H; brs); 6,98 (2H; d; J = 8,1 Hz); 7,21 (2H; d; J = 8,1 Hz).

2) El dihidrocloruro de etil 1-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}piperidin-4-carboxilato (8,2 mg; rendimiento 43%) fue obtenido como un polvo blanco del etil 1-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}piperidin-4-carboxilato (20 mg; 0,0354 mmol) según un método similar al método del Ejemplo 2-3).

EIMS(M+1):466

Ejemplo 422

Dihidrocloruro de ácido 1-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}piperidin-4-

carboxílico

1) El ácido 1-{[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}piperidin-4-carboxílico (240 mg, rendimiento 87%) fue obtenido como un polvo blanco del etil 1-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}piperidin-4-carboxilato (290 mg; 0,513 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:1,01 (6H; d; J = 6,4 Hz); 1,37 (9H; s); 1,48-1,62 (1H; m); 1,73 (1H; d; J = 11,1 Hz); 1,89 (1H; d; J = 10,6 Hz); 2,14-2,29 (1H; m); 2,40 (3H; s); 2,74 (3H; s); 2,77-3,00 (2H; m); 3,06 (2H; d; J = 6,0 Hz); 3,42 (2H; s); 3,53 (1H; d; J = 12,8 Hz); 4,10 (2H; d; J = 5,09 Hz); 4,20 (1H; brs); 4,26 (1H; d; J = 12,6 Hz); 4,65 (1H; s); 7,01 (2H; d; J = 7,5 Hz); 7,27 (2H; d; J = 7,5 Hz).

2) Dihidrocloruro de ácido 1-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}piperidin-4-carboxílico (220 mg, rendimiento 100%) fue obtenido como un polvo blanco del ácido 1-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}piperidin-4-carboxílico (230 mg; 0,428 mmol) según un método similar al método del Ejemplo 2-3).

EIMS(M+1):438

Ejemplo 423

Dihidrocloruro de N-2-adamantil-2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetamida

1) Terc-butil {[5-[2-(2-adamantilamino)-2-oxoetil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (50 mg, rendimiento 13%) fue obtenido como un polvo blanco de ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetico (300 mg; 0,703 mmol) y del 2-adamantanamina (396 mg; 2,11 mmol) según un método similar al método del Ejemplo 311-1).

^{1}H-RMN ($CDCl_3$) δ:0,95 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 1,53-1,63 (2H; m); 1,67-1,84 (9H; m); 2,12-2,26 (1H; m); 2,39 (3H; s); 2,57 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,30 (2H; s); 3,97 (2H; d; J = 8,1 Hz); 4,06 (2H; d; J = 5,09 Hz); 4,20 (1H; brs); 4,22 (1H; s); 5,45 (1H; d; J = 8,3 Hz); 6,96 (2H; d; J = 7,9 Hz); 7,22 (2H; d; J = 7,9 Hz).

2) Dihidrocloruro de N-2-Adamantil-2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetamida (45,1 mg; rendimiento 100%) fue obtenido como un polvo blanco del terc-butil {[5-[2-(2-adamantilamin)-2-oxoetil]-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (48 mg; 0,0857 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,4 Hz); 1,47 (2H; d; J =

12,1 Hz); 1,63-1,94 (12H; m); 2,08-2,26 (1H; m); 2,40 (3H; s); 2,80 (3H; s); 3,22 (2H; d; J = 5,84 Hz); 3,44 (2H; s); 3,81 (2H; s); 7,19 (2H; d; J = 7,9 Hz); 7,34 (2H; d; J = 7,9 Hz); 7,87 (1H; d; J = 7,7 Hz); 8,49 (3H; brs).

Ejemplo 424

Dihidrocloruro de 2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-N-(2-tienilmetil)acetamida

1) El ácido [5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetico (500 mg; 1,17 mmol) y tiofen-2-metilamina (133 mg; 1,17 mmol) fue disuelto en tetrahidrofurano (5 mL) y fue agregado cianofosforato de dietilo (286 mg; 1,75 mmol) bajo efriamiento con hielo. La mezcla obtenida de la reacción fue agitada a temperatura ambiente por 16 hrs. La mezcla de reacción fue vertida en solución salina saturada, y la mezcla se extrajo con acetato de etilo. El extracto fue lavado con carbonato hidrógeno de sodio acuoso saturado y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar terc-butil [(2-isobutil-6-metil-4-(4-metilfenil)-5-{2-oxo-2-[(2-tienilmetil)amino]etil}piridin-3-il)metil]carbamato (493 mg; rendimiento 81%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,96 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,11-2,27 (1H; m); 2,37 (3H; s); 2,56 (3H; s); 2,76 (2H; d; J =

7,2 Hz); 3,30 (2H; s); 4,03 (2H; d; J = 4,9 Hz); 4,20 (1H; brs); 4,51 (2H; d; J = 5,7 Hz); 6,85-7,00 (4H; m); 7,16 (2H; d; J = 7,9 Hz); 7,23 (1H; dd; J = 5,1; 1;1 Hz).

2) El dihidrocloruro de 2-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-N-(2-tienilmetil)acetamida (300 mg, rendimiento 66%) fue obtenido como un polvo blanco del terc-butil [(2-isobutil-6-metil-4-(4-metilfenil)-5-{2-oxo-2-[(2-tienilmetil)amino]etil}piridin-3-il)metil]carbamato (480 mg; 0,92 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,6 Hz); 2,12-2,33 (1H; m); 2,37 (3H; s); 2,47 (3H; s); 2,59 (2H; s); 3,28 (2H; s); 3,76 (2H; s); 4,37 (2H; d; J = 5,8 Hz); 6,89-6,94 (1H; m); 6,97 (1H; dd; J = 5,0; 3,5 Hz); 7,43 (1H; dd; J = 5,0; 1,2 Hz); 8,04 (3H; brs).

Ejemplo 425

Trihidrocloruro de 2-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-N-(piridin-3-ilmetil)acetamida

1) El terc-butil [(2-isobutil-6-metil-4-(4-metilfenil)-5-{2-oxo-2-[(piridin-3-ilmetil)amino]etil}piridin-3-il)metil]carbamato (394 mg, rendimiento 65%) fue obtenido como un polvo blanco del ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetico (500 mg; 1,17 mmol) y del 3-(aminometil)piridina (133 mg, 1.17 mmol) según un método

similar al método del Ejemplo 424-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,37 (9H; s); 2,14-2,29 (1H; m); 2,38 (3H; s); 2,55 (3H; s); 2,75 (2H; d; J = 7,2 Hz); 4,02 (2H; d; J = 4,9 Hz); 4,20 (1H; brs); 4,35 (2H; d; J = 5,8 Hz); 5,47 (1H; s); 6,88 (2H; d; J = 7,9 Hz); 7,15 (2H; d; J = 7,7 Hz); 7,54 (1H; d; J = 7,7 Hz); 8,45 (1H; d; J = 1,5 Hz); 8,55 (1H; dd; J = 4,7; 1,3 Hz).

2) El Trihidrocloruro 2-[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-N-(piridin-3-ilmetil)acetamida (380 mg, rendimiento 98%) fue obtenido como un polvo blanco del terc-butil [(2-isobutil-6-metil-4-(4-metilfenil)-5-{2-oxo-2-[(piridin-3-ilmetil)amino]etil}piridin-3-il)metil]carbamato (380 mg; 0,74 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,11-2,24 (1H; m); 2,40 (3H; s); 2,78 (3H; s); 3,20 (2H; d; J = 7,4 Hz); 3,43 (2H; s); 4,37 (2H; d; J = 5,7 Hz); 7,16 (2H; d; J = 8,1 Hz); 7,33 (2H; d; J = 8,1 Hz); 8,00 (1H; dd; J = 8,0; 5,6 Hz); 8,28 (1H; d; J = 8,1 Hz); 8,48 (3H; brs); 8,70-8,77 (1H; m); 8,80-8,85 (1H; m).

Ejemplo 426

Dihidrocloruro de metil 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)tiofin-3-carboxilato

1) El ácido[5-{[(terc-Butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetico (500 mg; 1,17 mmol), el metil 4-aminotiofin-3-carboxilato (184 mg; 1,17 mmol) y el hexafluorfosfato de 0-(7-azabencetriazol-1-il)-1,1,3,3-tetrametiluronio (HATU, 1,0 g; 1,75 mmol) fue disuelto en N,N-dimetilformamida (10 mL) y la mezcla fue agitada a la temperatura ambiente por 24 hrs. La mezcla de reacción fue vertida en solución salina saturada, y la mezcla se extrajo con acetato de etilo. El extracto fue lavado con carbonato hidrógeno de sodio acuoso saturado y fue secado sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo fue purificado por cromatografía en columna de gel de sílice para dar metil 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)tiofin-3-carboxilato (440 mg, rendimiento 66%) como un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,4 Hz); 1,40 (9H; s); 2,24-2,33 (1H; m); 2,35 (3H; s); 2,53 (3H; s); 2,77 (2H; d; J = 7,2 Hz); 3,52 (2H; s); 3,79 (3H; s); 4,06 (2H; d; J = 4,1 Hz); 4,20 (1H; brs); 7,02 (2H; d; J = 7,9 Hz); 7,17 (2H; d; J = 7,9 Hz); 7,95-7,98 (1H; m); 7,98-8,02 (1H; m).

2) Dihidrocloruro de metil 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)tiofin-3-carboxilato (161 mg, rendimiento 65%) fue obtenido como un polvo blanco de metil 4-({[5-{[(terc-

butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)tiofin-3-carboxilato (262 mg; 0,46 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,6 Hz); 2,11-2,27 (1H; m); 2,35 (3H; s); 2,48 (3H; s); 2,80 (2H; s); 3,14 (2H; s) 3,76-3,86 (5H; m); 7,17 (2H; d; J = 7,9 Hz); 7,32 (2H; d; J = 7,9 Hz); 7,80 (1H; d; J = 3,2 Hz); 8,26-8,45 (3H brs); 9,69 (s, 1H).

Ejemplo 427

Dihidrocloruro de ácido 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)tiofin-3-carboxílico

1) El ácido 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)tiofin-3-carboxílico (183 mg, rendimiento 67%) fue obtenido como un polvo blanco de metil 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)tiofin-3-carboxilato (280 mg; 0,495 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,40 (9H; s);2,11-2,24 (1H;m); 2,36 (3H; s); 2,52 (3H; s); 2,78 (2H; s); 3,49 (2H; s); 4,03 (2H; s); 4,20 (1H; brs); 6,98-7,25 (4H; m);

7,85-8,05 (2H; m).

2) El dihidrocloruro de ácido 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)tiofen-3-carboxílico (143 mg, rendimiento 64%) fue obtenido como un polvo blanco del ácido 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)tiofin-3-carboxílico (170 mg; 0,428 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,11-2,27 (1H; m); 2,35 (3H; s); 2,50 (3H; s); 2,79 (2H; s); 3,14 (2H; s); 3,81 (2H; s); 7,17 (2H; d; J = 8,1 Hz); 7,30 (2H; d; J = 8,1 Hz); 7,79 (1H; d; J = 3,6 Hz); 8,29 (1H; d; J = 3,6 Hz); 8,33-8,44 (3H, s); 9,89 (1H; s).

Ejemplo 428

Dihidrocloruro de metil 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoato

1) El metil 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoato (442 mg, rendimiento 67%) fue obtenido como un polvo blanco del ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetico (500 mg; 1,17 mmol) y del metil 4-aminobenzoato (177 mg; 1,17 mmol) según un método similar al método del Ejemplo 426-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,38 (9H; s); 2,15-2,28 (1H; m); 2,63 (3H; s); 2,77 (2H; d; J = 7,4 Hz); 3,47 (2H; s); 3,89 (3H; s); 4,06 (2H; d; J = 5,1 Hz); 4,20 (1H; brs); 7,01 (2H; d; J = 7,9 Hz); 7,23 (2H; d; J = 7,9 Hz); 7,42 (2H; d; J = 8,7 Hz); 7,97 (2H; d; J = 8,7 Hz).

2) El dihidrocloruro de metil 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoato (142 mg, rendimiento 97%) fue obtenido como un polvo blanco del metil 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoato (154 mg; 0,275 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,10-2,30 (1H; m); 2,36 (3H; s); 2,49 (3H; s); 2,71 (2H; s); 3,01 (2H; s); 3,77 (2H; s); 3,82 (3H; s); 7,17 (2H; d; J = 8,1 Hz); 7,32 (2H; d; J = 8,1 Hz); 7,62 (2H; d; J = 8,9 Hz); 7,90 (2H; d; J = 8,9 Hz);, 8,15 (3H; brs).

Ejemplo 429

Dihidrocloruro de ácido 4-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoico

1) El ácido 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoico (275 mg, rendimiento 100%) fue obtenido como un polvo blanco del metil 4-({[5-{[(terc-

butoxicarbonil)amino]metil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoato (280 mg; 0,500 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN ($CDCl_3$) δ:0,99 (6H; d; J = 6,2 Hz); 1,37 (9H; s); 2,12-2,27 (1H; m); 2,35 (3H; s); 2,87 (3H; s); 3,19 (2H; s); 3,87 (2H; s); 4,15 (2H; d; J = 6,2 Hz); 4,20 (1H; brs); 7,10 (2H; d; J = 8,1 Hz); 7,25 (2H; d; J = 8,1 Hz); 7,68 (2H; d; J = 8,5 Hz); 8,68 (2H; d; J = 8,5 Hz).

2) El dihidrocloruro de ácido 4-({[5-(Aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoico (235 mg, rendimiento 92%) fue obtenido como un polvo blanco del ácido 4-({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoico (270 mg; 0,495 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:1,00 (6H; d; J = 6,6 Hz); 2,12-2,28 (1H; m); 2,37 (3H; s); 2,50 (3H; s); 2,80 (2H; s); 3,15 (2H; s); 3,82 (2H; s); 7,20 (2H; d; J = 8,1 Hz); 7,34 (2H; d; J = 8,1 Hz); 7,60 (2H; d; J = 8,9 Hz); 7,87 (2H; d; J = 8,9 Hz); 8,35 (3H; brs).

Ejemplo 430

Dihidrocloruro de etil 2-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]-1,3-tiazol-4-carboxilato

1) El etil 2-({[(benciloxi)carbonil]amino}metil)-1,3-tiazol-4-carboxilato (3,5 g; 10,9 mmol) fue disuelto en solución al 30% de ácido hidrógeno bromuro acético (50 mL), y la solución fue agitada a temperatura ambiente por 2 hrs. El precipitado blanco fue recolectado por filtración y fue disuelto en el carbonato de hidrógeno de sodio acuoso saturado. La solución obtenida fue concentrada bajo presión reducida, y el residuo fue disuelto en el acetato de etilo. El material insoluble fue filtrado y el filtrado fue concentrado bajo presión reducida para dar etil 2-(aminometil)-1,3-tiazol-4-carboxilato (793 mg, rendimiento 40%) como un aceite. El etil 2-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]-1,3-tiazol-4-carboxilato (649 mg, rendimiento 100%) fue obtenido como un polvo blanco del aceite (793 mg) y del ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetico (454 mg; 1,07 mmol) según un método similar al método del Ejemplo 424-1).

^{1}H-RMN ($CDCl_3$) δ:0,97 (6H; d; J = 6,6 Hz); 1,35-1,47 (12H; m); 2,13-2,28 (1H; m); 2,36 (3H; s); 2,53 (3H; s); 2,75 (2H; d; J = 7,2 Hz); 3,34 (2H; s); 4,03 (2H; d; J = 5,3 Hz); 4,20 (1H; brs); 4,43 (2H; q; J = 7,2 Hz); 4,66 (2H; d; J = 6,0 Hz); 6;93 (2H; d; J = 7,9 Hz); 7,14 (2H; d; J = 7,9 Hz); 8,14 (1H; s).

2) El dihidrocloruro de etil 2-[({[5-(aminometil)-6-isobutil-

2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]-1,3-tiazol-4-carboxilato (138 mg, rendimiento 81%) fue obtenido como un polvo blanco del etil 2-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]-1,3-tiazol-4-carboxilato (178 mg; 0,299 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,98 (6H; d; J = 6,4 Hz); 1,31 (3H; t; J = 7,2 Hz); 2,10-2,23 (1H; m); 2,38 (3H; s); 2,49 (3H; s); 2,77 (2H; s); 3,14 (2H; s); 3,41 (2H; s); 3,80 (2H; s); 4,31 (2H; q; J = 7,2 Hz); 4,51 (2H; d; J = 5,8 Hz); 7,17 (2H; d; J = 8;1 Hz); 7,32 (2H; d; J = 8,1 Hz); 8,36 (3H; brs); 8,91 (1H; s).

Ejemplo 431

Dihidrocloruro de ácido 2-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]-1,3-tiazol-4-carboxílico

1) El ácido 2-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]-1,3-tiazol-4-carboxílico (438 mg; rendimiento 100%) fue obtenido como un polvo blanco del etil 2-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]-1,3-tiazol-4-carboxilato (460 mg; 0,773 mmol) según un método similar al método del Ejemplo 9-1).

^{1}H-RMN($CDCl_3$) δ: 0,93 (6H; d; J = 6,6 Hz); 1,34 (9H; s); 2,09-2,26 (1H; m); 2,34 (3H; s); 2,40 (2H; s); 2,48 (3H; s); 3,24 (2H; s); 3,80 (2H; s); 4,20 (1H; brs); 4,48 (2H; d; J = 5,8 Hz); 7,09 (2H; d; J = 7,0 Hz); 7,19 (2H; d; J = 7,0 Hz); 8,39 (1H; s).

2) El dihidrocloruro de ácido 2-[({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]-1,3-tiazol-4-carboxílico (235 mg, rendimiento 91%) fue obtenido como un polvo blanco del ácido 2-[({[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)metil]-1,3-tiazol-4-carboxílico (270 mg; 0,495 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ: 1,00 (6H; d; J = 6,6 Hz); 2,12-2,28 (1H; m); 2,37 (3H; s); 2,50 (3H; s); 2,80 (2H; s); 3,15 (2H; s); 3,82 (2H; s); 7,20 (2H; d; J = 8,1 Hz); 7,34 (2H; d; J = 8,1 Hz); 7,60 (2H; d; J = 8,9 Hz); 7,87 (2H; d; J = 8,9 Hz); 8,35 (3H; brs).

Ejemplo 432

Dihidrocloruro de metil 1-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}prolinato

1) El metil 1-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}prolinato (456 mg, rendimiento 72%) fue obtenido

como un polvo blanco del ácido [5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetico (500 mg; 1,17 mmol) y monohidrocloruro de metil prolina (194 mg; 1,17 mmol) según un método similar al método del Ejemplo 426-1).

^{1}H-RMN ($CDCl_3$) δ:0,98 (6H; d; J = 6,6 Hz); 1,37 (9H; s); 1,84-2,00 (3H; m); 2,05 (3H; s); 2,08-2,24 (2H; m); 2,75 (3H; s); 3,15-3,26 (2H; m); 3,48 (2H; s); 3,71 (3H; s); 4,11-4,21 (3H; m); 4,31-4,55 (2H; m); 7,02-7,15 (2H; m); 7,28-7,41 (2H; m).

2) El dihidrocloruro de metil 1-{[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}prolinato (277,5 mg; rendimiento 64%) fue obtenido como un polvo blanco de metil 1-{[5-{[(terc-butoxicarbonil)amino]metil}-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}prolinato (456 mg; 0,848 mmol) según un método similar al método del Ejemplo 2-3).

^{1}H-RMN (DMSO-d_6) δ:0,97 (6H; d; J = 6,4 Hz); 1,76-1,91 (3H; m); 2,04-2,24 (2H; m); 2,40 (3H; s); 2,65 (3H; s); 2,96 (2H; s); 3,17 (2H; t; J = 6,7 Hz); 3,42 (2H; s); 3,61 (3H; s); 3,77 (2H; s); 4,19-4,32 (2H; m); 7,15 (2H; d; J = 7,4 Hz); 7,37 (2H; d; J = 7,4 Hz); 8,10 (3H; s).

Ejemplo 433

Dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-3-(5-oxo-4,5-dihidro-1,2,4-

oxadiazol-3-il)benzamida

A una solución de terc-butil {[5-amino-2-isobutil-6-metil-4-(4-metilfenil)piridin-3-il]metil}carbamato (383 mg; 1,0 mmol) en tetrahidrofurano (5 mL) fue agregado cloruro de 3-cianobenzoilo (245 mg; 1,5 mmol) y fue agregado trietilamina (280 µL; 2,0 mmol). La mezcla fue agitada por 18 hrs. Solución acuosa saturada de carbonato hidrógeno de sodio (5 mL) fue agregada a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de sílice para dar un aceite. A una solución del aceite obtenido en el etanol (5 mL) fue agregado el hidrocloruro de hidroxilamina (192 mg; 3,0 mmol) y carbonato de sodio (420 mg; 4,0 mmol) y la mezcla fue agitada a 80°C por 15 hrs. Agua destilada (10 mL) fue agregada a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida para dar un aceite. A una solución del aceite obtenido en tetrahidrofurano (3 mL) fue agregado N,N'-carbonildiimidazol (324 mg; 2,0 mmol) y la mezcla fue agitada a 65°C por 2 hrs. Solución acuosa saturada de carbonato de sodio (5 mL) fue

agregada a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con solución salina saturada y fue secada sobre sulfato de magnesio anhidro. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue purificado por cromatografía en columna de gel de silice para dar un aceite. A una solución del aceite obtenido en el acetato de etilo (2 mL) fue agregado solución 4N de acetato de etil cloruro hidrógeno (2 mL) y la mezcla fue agitada a la temperatura ambiente por 3 hrs. El solvente fue evaporado bajo presión reducida y el residuo obtenido fue cristalizado del hexano para dar dihidrocloruro de N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]-3-(5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-il)benzamida (115 mg, rendimiento 21%) como un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ:0,99 (6H; d; J = 6,6 Hz); 2,21-2,29 (1H; m); 2,29 (3H; s); 2,50 (3H; s); 2,96 (2H; s); 3,82 (2H; s); 7,21 (4H; s); 7,62 (1H; t; J = 7,5 Hz); 7,79 (1H; d; J = 7,5 Hz); 7,93 (1H; d; J = 7,5 Hz); 8,25 (3H; brs); 10,13 (1H; brs); 13,12 (1H; brs).

Ejemplo experimental 1

Determinación de actividad inhibitoria de dipeptidil peptidasa IV en el plasma de rata

La reacción fue realizada según el método de Raymond y col. ("Diabetes", vol. 47, pág. 1253-1258, 1998) usando una

placa de 96 hendiduras de fondo plano a 30°C. Una solución de N,N-dimetilformamida (1 µL) conteniendo el compuesto de prueba fue agregada a una mezcla de agua (69 mL),. amortiguador 1 M Tris-clorhidrato (10 µL, pH 7,5) y 1 mM solución acuosa de Gly-Pro-p-NA (100 µL) para preparar una solución mixta. El Plasma (20 µL) preparado de sangre de rata SD por un método convencional fue agregado a la solución mixta indicada precedentemente y la reacción de la enzima fue comenzada a 30°C. La absorbencia después de 0 hr. y 1 hr. fue medida usando un lector de microplaca a una longitud de onda de 405 nm y fue determinado el incremento (ΔODs). Al mismo tiempo, un incremento (ΔODc) en la absorbencia de la mezcla de reacción sin el compuesto de prueba, y un incremento (ΔODb) en la absorbencia de la mezcla de reacción sin el compuesto de prueba y la enzima fue determinada y el por ciento de inhibición de actividad de la enzima dipeptidil peptidasa IV fue calculada con la fórmula siguiente:

$$\{1-[(\Delta ODs-\Delta ODb)/(\Delta ODc-\Delta ODb)]\}\times 100$$

La actividad inhibitoria de dipeptidil peptidasa IV del grupo de compuesto de prueba se expresa en valor IC_{50} (nM) y se ilustra en Tabla 5.

Tabla 5

Compuesto de prueba (Ejemplo No.)	valor IC_{50} (nM)
1	520

Según lo ilustrado anteriormente, el compuesto de la presente invención posee una actividad inhibitoria de dipeptidil peptidasa IV superior, y es útil como un agente para profilaxis o tratamiento de diabetes y lo similar.

Ejemplo experimental 2

Determinación de actividad inhibitoria de dipeptidil peptidasa IV en plasma de rata

De la misma manera como en el Ejemplo experimental 1, fue determinada la actividad inhibitoria de dipeptidil peptidasa IV del compuesto de prueba. Los resultados se ilustran en Tabla 6.

Tabla 6

Compuesto de prueba (Ejemplo No.)	valor IC_{50} (nM)
13	25
22	12
26	5,1
40	56
170	100
210	12
267	7,4
305	3,5
312	20
336	19
350	15
421	16
422	7,3

Según lo expresado precedentemente, el compuesto de la presente invención posee una actividad inhibitoria de

dipeptidil peptidasa IV superior, y por consiguiente, es útil como agente para profilaxis o tratamiento de diabetes y lo similar.

Ejemplo de formulación 1 (producción de cápsulas)

1) Compuesto de Ejemplo 1	30 mg
2) Polvo de celulosa fino	10 mg
3) Lactosa	19 mg
4) Estearato de magnesio	1 mg
total	60 mg

1), 2), 3) y 4) se mezclan y rellenan en cápsulas de gelatina.

Ejemplo de formulación 2 (producción de tabletas)

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
total de 1000 tabletas	140 g

Las cantidades completas de 1), 2) y 3), y 30 g de 4) fueron amasados con agua, secados al vacío y granulados. Los gránulos fueron mezcladoos con 14 g de 4) y 1 g de 5) y la mezcla fue comprimida con una máquina de formación de tableta, con la cual se obtienen 1000 tabletas que contienen 30 mg del compuesto del Ejemplo 1 por tableta.

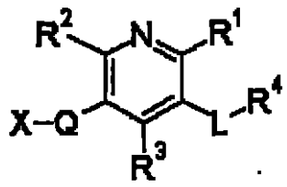
Aplicabilidad industrial

El compuesto de la presente invención presenta una actividad inhibitoria de peptidasa superior y es útil como agente para profilaxis o tratamiento de diabetes y lo similar.

Esta aplicación está basada en la solicitud de patente Nos. 373776/2003, 30491/2004 y 165977/2004 registrada en Japón, cuyo contenido es incorporado a la presente como referencia.

REIVINDICACIONES

1. Un compuesto representado por la fórmula



caracterizado por que

R^1 y R^2 son iguales o diferentes y cada uno es un grupo de hidrocarburo opcionalmente sustituido o un grupo hidroxilo opcionalmente sustituido;

R^3 es un grupo aromático opcionalmente sustituido;

R^4 es un grupo amino opcionalmente sustituido;

L es un grupo de hidrocarburo de cadena bivalente;

Q es un enlace o un grupo hidrocarburo de cadena bivalente; y

X es un átomo de hidrógeno, un grupo ciano, un grupo nitro, un grupo acilo, un grupo hidroxilo sustituido, un grupo tiol opcionalmente sustituido, un grupo amino opcionalmente sustituido o un grupo cíclico opcionalmente sustituido;

con la condición que

cuando X es un grupo etoxicarbonilo, entonces Q es un grupo hidrocarburo de cadena bivalente, y el compuesto no es

2,6-diisopropil-3-metilaminometil-4-(4-fluorofenil)-5-pentilpiridina;

2,6-diisopropil-3-aminometil-4-(4-fluorofenil)-5-pentilpiridina;

2,6-diisopropil-3-(dimetilamino)metil-4-(4-fluorofenil)-5-pentilpiridina;

2,6-diisopropil-3-(etilamino)metil-4-(4-fluorofenil)-5-pentilpiridina; y

3-(terc-butildimetilsililoximetil)-2;6-diisopropil-4-(4-fluorofenil)-5-(indolil-5-aminometil)piridina;

o una sal del mismo.

2. Un compuesto de acuerdo con la reivindicación 1, caracterizado por que R^1 y R^2 son iguales o diferentes y cada uno es un grupo hidrocarburo opcionalmente sustituido, y X es un grupo ciano, un grupo nitro, un grupo acilo, un grupo hidroxilo sustituido, un grupo tiol opcionalmente sustituido o un grupo cíclico opcionalmente sustituido.

3. Un compuesto de acuerdo con la reivindicación 1, caracterizado por que el grupo acilo para X es un grupo carbonilo.

4. Un compuesto de acuerdo con la reivindicación 1, caracterizado por que R^1 y R^2 son iguales o diferentes y cada uno es un grupo alquilo C_{1-10} opcionalmente sustituido por 1 a 3 sustituyente(s) seleccionados de un grupo cicloalquilo C_{3-10}, un grupo alcoxicarbonilo C_{1-6} y un grupo alcoxilo C_{1-6}.

5. Un compuesto de acuerdo con la reivindicación 1, caracterizado por que R^3 es un grupo arilo C_{6-14} opcionalmente

sustituido por 1 a 3 sustituyente(s) seleccionado(s) de un grupo alquilo C_{1-6} opcionalmente sustituido por 1 a 3 átomo(s) halógenos y un átomo halógeno.

6. Un compuesto de acuerdo con la reivindicación 1, caracterizado por que R^4 es un grupo amino.

7. Un compuesto de acuerdo con la reivindicación 1, caracterizado por que L es un grupo alquileno C_{1-10}.

8. Un compuesto de acuerdo con la reivindicación 1, caracterizado por que Q es un enlace.

9. Un compuesto de acuerdo con la reivindicación 1, caracterizado por que X es un grupo acilo, un grupo hidroxilo sustituido, un grupo tiol opcionalmente sustituido o un grupo amino opcionalmente sustituido.

10. Un compuesto de acuerdo con la reivindicación 1, caracterizado por que X es un grupo carbonilo.

11. Un compuesto de acuerdo con la reivindicación 1, caracterizado por que es ácido 5-(aminometil)-2-metil-4-(4-metilfenil)-6-neopentilnicotínico;

ácido 5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)nicotínico;

metil 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]metoxi}-1-metil-1H-pirazol-4-carboxilato;

{[2-isobutil-6-metil-4-(4-metilfenil)-5-(2-morfolin-4-il-2-oxoetil)piridin-3-il]metil}amina;

metil 3-({[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]acetil}amino)benzoato;

N-[5-(aminometil)-6-isobutil-2-metil-4-(4-metilfenil)piridin-3-il]isoxazol-4-carboxamida,

o una sal del mismo.

12. Una prodroga caracterizada por que es de un compuesto de acuerdo con la reivindicación 1 o una sal del mismo.

13. Un agente farmacéutico caracterizado por que comprende un compuesto de acuerdo con la reivindicación 1 o una sal del mismo o una prodroga del mismo.

14. Un agente farmacéutico de acuerdo con la reivindicación 13, caracterizado por que es un agente para profilaxis o tratamiento de diabetes, complicaciones diabéticas, tolerancia a glucosa disminuida u obesidad.

15. Un inhibidor de peptidasa caracterizado por que comprende un compuesto de acuerdo con la reivindicación 1 o una sal del mismo o una prodroga del mismo.

16. Un inhibidor de acuerdo con la reivindicación 15, caracterizado por que la dipeptidil peptidasa es dipeptidasa-IV.

17. Una aplicación de un compuesto de acuerdo con la reivindicación 1 o una sal del mismo o una prodroga del mismo caracterizado por que se indica para producción de un agente para profilaxis o tratamiento de diabetes, complicaciones

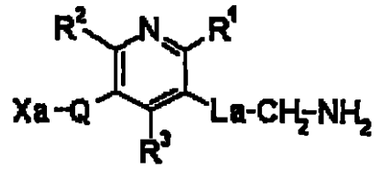
diabéticas, tolerancia de glucosa disminuída u obesidad.

18. Una aplicación de un compuesto de acuerdo con la reivindicación 1 o una sal del mismo o una prodroga del mismo caracterizado por que se indica para producción de un inhibidor de peptidasa.

19. Un método para profilaxis o tratamiento de diabetes, complicaciones diabéticas, tolerancia de glucosa disminuída u obesidad en un mamífero caracterizado por que comprende administrar al mamífero un compuesto de acuerdo con la reivindicación 1 o una sal del mismo o una prodroga del mismo.

20. Un método para inhibir la peptidasa en un mamífero caracterizado por que comprende administrar al mamífero un compuesto de acuerdo con la reivindicación 1 o una sal del mismo o una prodroga del mismo.

21. Un método de producción de un compuesto representado por la fórmula



(I-a)

caracterizado por que

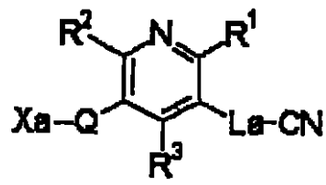
R^1, R^2, R^3 y Q

son iguales a los definidos en la reivindicación 1;

La es un enlace o un grupo de hidrocarburo de cadena bivalente; y

Xa es un átomo de hidrógeno, un grupo nitro, un grupo acilo, un grupo hidroxilo sustituido, un grupo tiol opcionalmente sustituido, un grupo amino opcionalmente sustituido o un grupo cíclico opcionalmente sustituido;

o una sal del mismo que comprende someter un compuesto representado por la fórmula



(II)

en donde cada símbolo es igual al definido anteriormente, o una sal del mismo a una reacción de reducción.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
09689		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/JP2004/016457	29/10/2004	31/10/2003
Applicant		
TAKEDA PHARMACEUTICAL COMPANY LIMITED		

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

This International Search Report consists of a total of 5 sheets.

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

1. Basis of the report
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.
2. [ ] Certain claims were found unsearchable (See Box II).
3. [ ] Unity of invention is lacking (see Box III).
4. With regard to the title,
   [ ] the text is approved as submitted by the applicant.
   [X] the text has been established by this Authority to read as follows:

   PYRIDINE COMPOUNDS AS INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

5. With regard to the abstract,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the drawings to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

INTERNATI NAL SEARCH REPORT

International Application No
PCT/JP2004/016457

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/80 C07D213/82 C07D213/56 C07D213/55 C07D401/12
C07D213/59 C07D401/06 C07D413/06 C07F9/40 C07D213/71
C07D213/75 C07D409/12 C07D405/12 C07D213/12 C07D413/12

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)
IPC 7 C07D C07F A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	US 6 218 431 B1 (SCHOEN WILLIAM R ET AL) 17 April 2001 (2001-04-17) cited in the application column 161; example 73 column 62; example CXLVI column 104; figure 7 column 189 - column 190; examples 120-123 column 66; table 2B	1-20
X	PATENT ABSTRACTS OF JAPAN vol. 013, no. 212 (P-873), 18 May 1989 (1989-05-18) -& JP 01 029979 A (MITSUBISHI ELECTRIC CORP), 31 January 1989 (1989-01-31) abstract examples 73-82,92-118	1-20
	-/—	

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 February 2005	17/02/2005
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Kollmannsberger, M

1

INTERNATIONAL SEARCH REP RT

International Application No
PCT/JP2004/016457

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SAMMOUR, A. ET AL: "Base catalyzed addition reaction with diaroyl ethylenes and some chalcones" XP002315994 retrieved from STN Database accession no. 1979:611215 compound with RN 71543-88-9 abstract & EGYPTIAN JOURNAL OF CHEMISTRY , VOLUME DATE 1976, 19(6), 989-1011 CODEN: EGJCA3; ISSN: 0367-0422, 1979,	1-11,13, 15
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PAVEL, G. V. ET AL: "Condensation of aldehydes and ketones. XVIII. Aminomethylation of methylene- and benzylidenediacetophenone" XP002315995 retrieved from STN Database accession no. 1968:496405 compound with RN 19731-37-4 abstract & KHIMIYA GETEROTSIKLICHESKIKH SOEDINENII , (3), 484-6 CODEN: KGSSAQ; ISSN: 0132-6244, 1968,	1-11,13, 15
X	EP 0 742 208 A (GRELAN PHARMACEUTICAL CO., LTD; LABORATOIRES FOURNIER S.C.A) 13 November 1996 (1996-11-13) page 24; examples 43,44	1-11,13, 15
A	WO 03/068757 A1 (F. HOFFMANN-LA ROCHE AG) 21 August 2003 (2003-08-21) cited in the application claims	1-21
A	US 2003/195188 A1 (BOEHRINGER MARKUS ET AL) 16 October 2003 (2003-10-16) claims	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2004/016457

Box 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.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19 and 20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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 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 an additional fee, this Authority did not invite payment of any additional fee.

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 additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP2004/016457

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 6218431	B1	17-04-2001	AU	3897197 A	20-02-1998
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			CA	2262434 A1	05-02-1998
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			CZ	9900308 A3	12-05-1999
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			HR	970425 A1	31-08-1998
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			WO	9634856 A1	07-11-1996
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			HU	9700005 A2	28-05-1998
			JP	10506922 T	07-07-1998
			NO	965459 A	18-12-1996
			US	5872115 A	16-02-1999
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			BR	0307665 A	04-01-2005
			CA	2474578 A1	21-08-2003
			EP	1476435 A1	17-11-2004
			US	2003216382 A1	20-11-2003
US 2003195188	A1	16-10-2003	AU	2003206834 A1	04-09-2003
			BR	0307576 A	11-01-2005
			CA	2474460 A1	21-08-2003
			WO	03068748 A1	21-08-2003
			EP	1476429 A1	17-11-2004

Folio 851 extracts

[redacted]

FORMATO DE DIGITALIZACIÓN
RELACION DE ANEXOS

Royal Technologies S.A.

851

Item	Expediente No	6050814 No de unidades	No de Folio √
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones: Acta Final

~~861~~
852

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-050514- -00000-0000
Fec: 2006-05-26 16:51:57 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEIYII
Ers: 376 FASENACIONALI
Act 411 PRESENTACION Folios: 852

RECIBO OFICIAL DE CAJA : 06 - 36,151
FECHA : MAYO 15 DE 2006

***** 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 POPULAR	050-00110-6	54982575	15/05/2006	47,972,500.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Colo 14656 841 009 7

853

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-050514- -00000-0000
Fec: 2006-05-25 16:51:57 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIYI
Cla: 375 FABRICACIONALI
Act 411 PRESENTACION Folios: 652

Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN (✓) MODELO DE UTILIDAD ( )	( )	( )
-Indicación de que se solicita la concesión de una patente.	(✓)	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	(✓)	( )
-Descripción de la invención.	(✓)	( )
-Dibujos de ser estos pertinentes.	( )	( )
-Comprobante de Pago de las tasas establecidas.	(✓)	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
DISEÑO INDUSTRIAL ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se 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 ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica del Esquema Trazado.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )

Firma Responsable: _____

Fecha: Mayo 25/06